X-Linked Hypophosphatemia in Adults
New Biology, New Therapies

September 16, 2016

Karl L. Insogna, MD
Ensign Professor of Medicine/Endocrinology
Yale School of Medicine

ale Bone Center

ASBMR

CONFLICT OF INTEREST

Karl Insogna

I am an investigator conducting clinical trials in patients with XLH and TIO sponsored by

Ultragenyx

ale Bone Center

ASBMR

Outline

- Review the key clinical and biochemical features of X-linked hypophosphatemia (XLH) in adults.
- Summarize the pathogenesis of XLH and the central role of FGF23 in this disease.
- Review the efficacy and limitations of treatment with calcitriol and supplemental phosphorus for XLH.
- Review the pre-clinical studies that support the use of a blocking antibody to FGF23 in the treatment of XLH.
- Report data from phase 2 studies using a recombinant human IgG_1 monoclonal antibody to FGF23 in adults with XLH.
- Speculate on future directions for the treatment of this disorder.

Background

- FGF23 is a hormone produced by osteocytes that inhibits renal tubular phosphate reabsorption, leading to renal phosphate wasting and hypophosphatemia.

- It suppresses production of $1,25(OH)_2$vitamin D, which impairs intestinal calcium and, to a lesser extent, phosphate absorption.

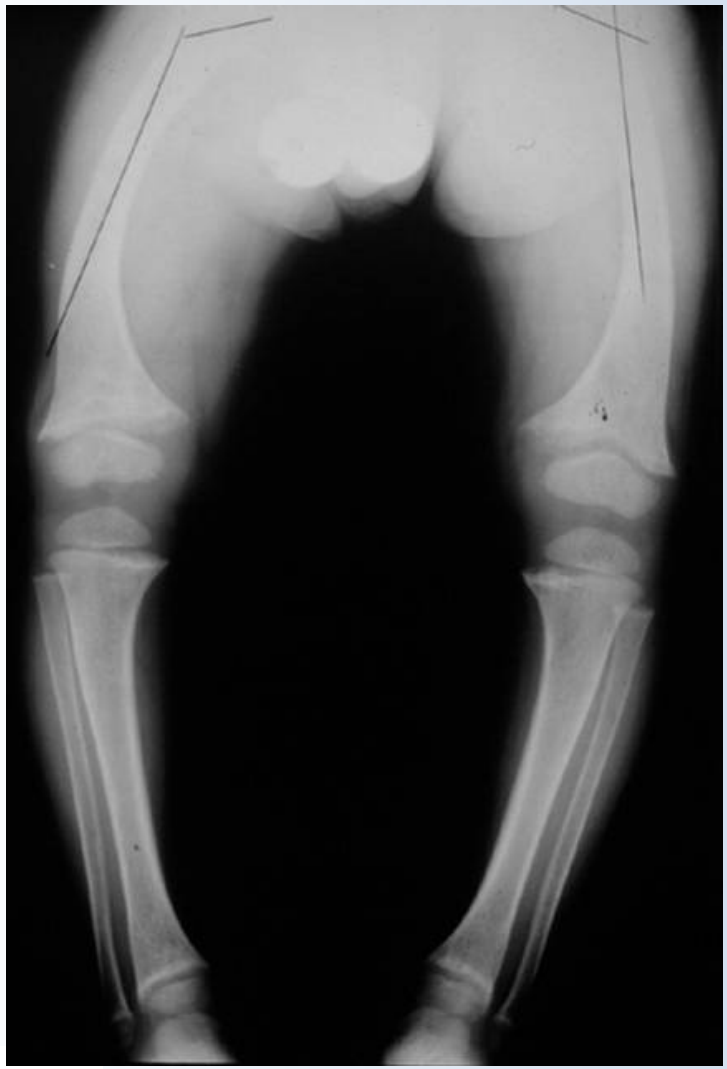
Background

- FGF23 is overproduced by osteocytes in the genetic disorder X-linked hypophosphatemia, which is characterized by short stature and rickets in children, osteomalacia in adults, and a variety of other skeletal problems.

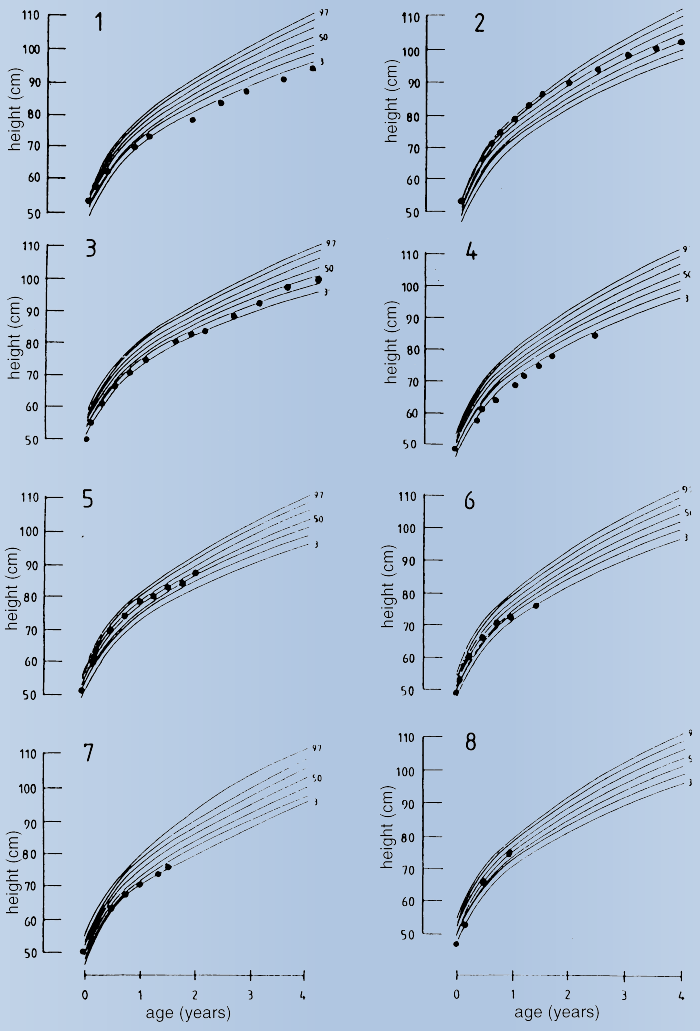
- The genetic basis for XLH is loss of function mutations in the enzyme, PHEX, which is located on the X chromosome.

Complications of XLH in Children that Impact Adults

Limb deformities



Short stature



ale Bone Center

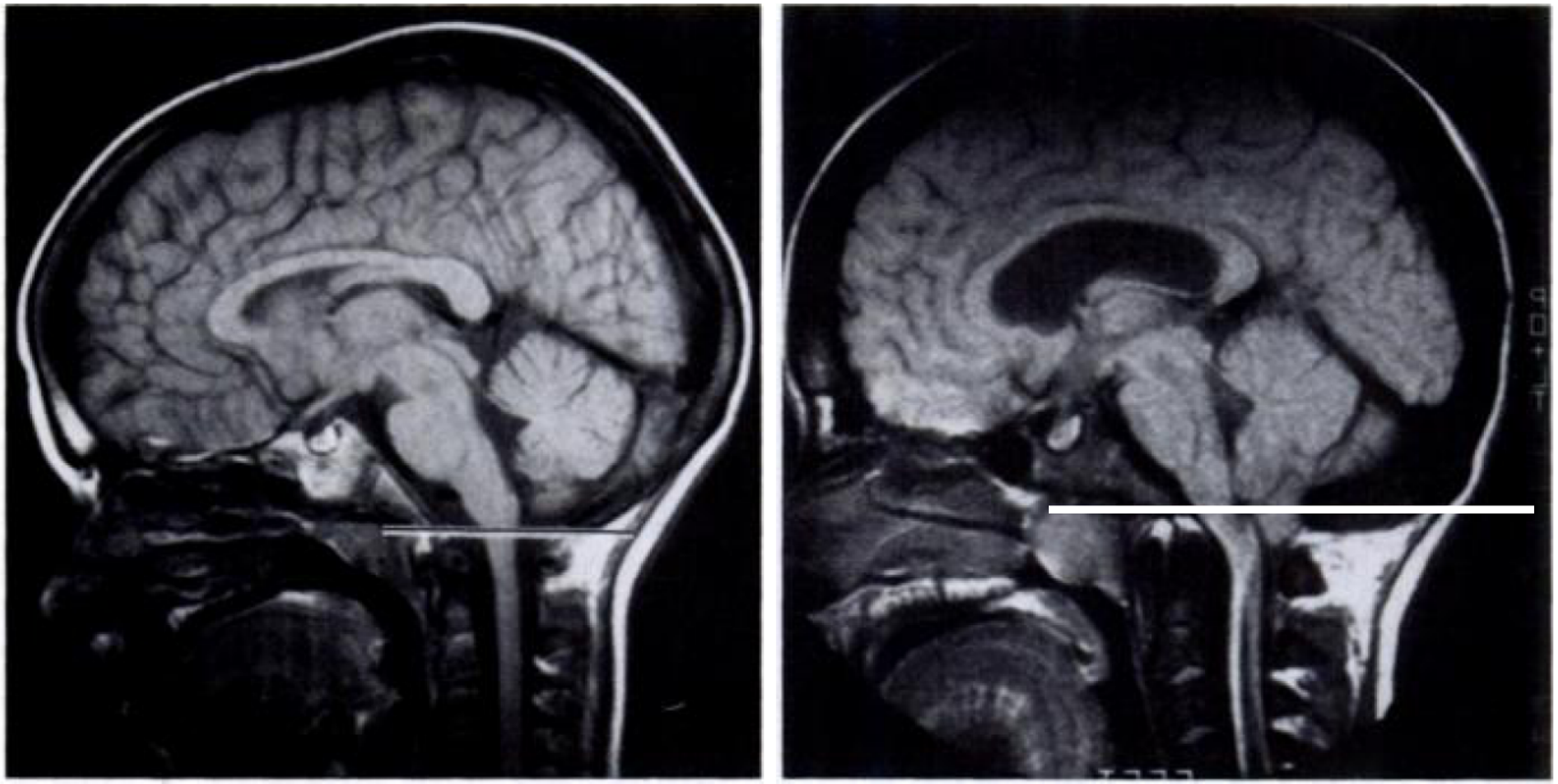
ASBMR

Complications of XLH in Children that Impact Adults

Cranial anomalies:

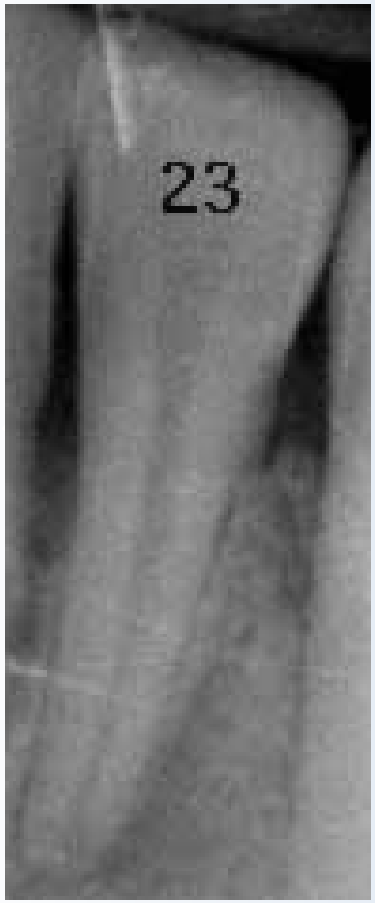
Craniosynostoses

Chiari malformations

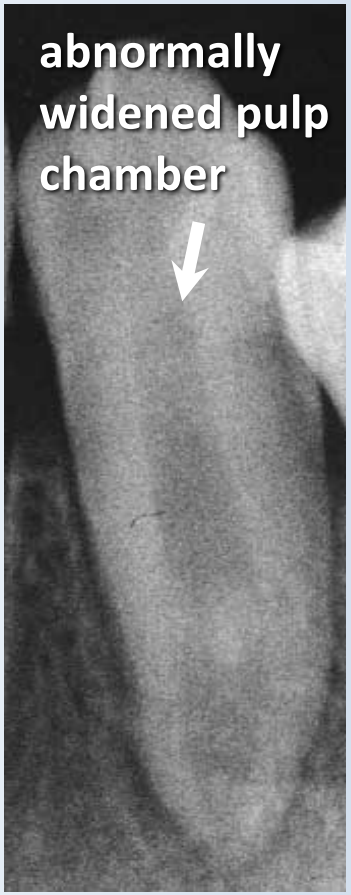


Complications of XLH : Dental Disease

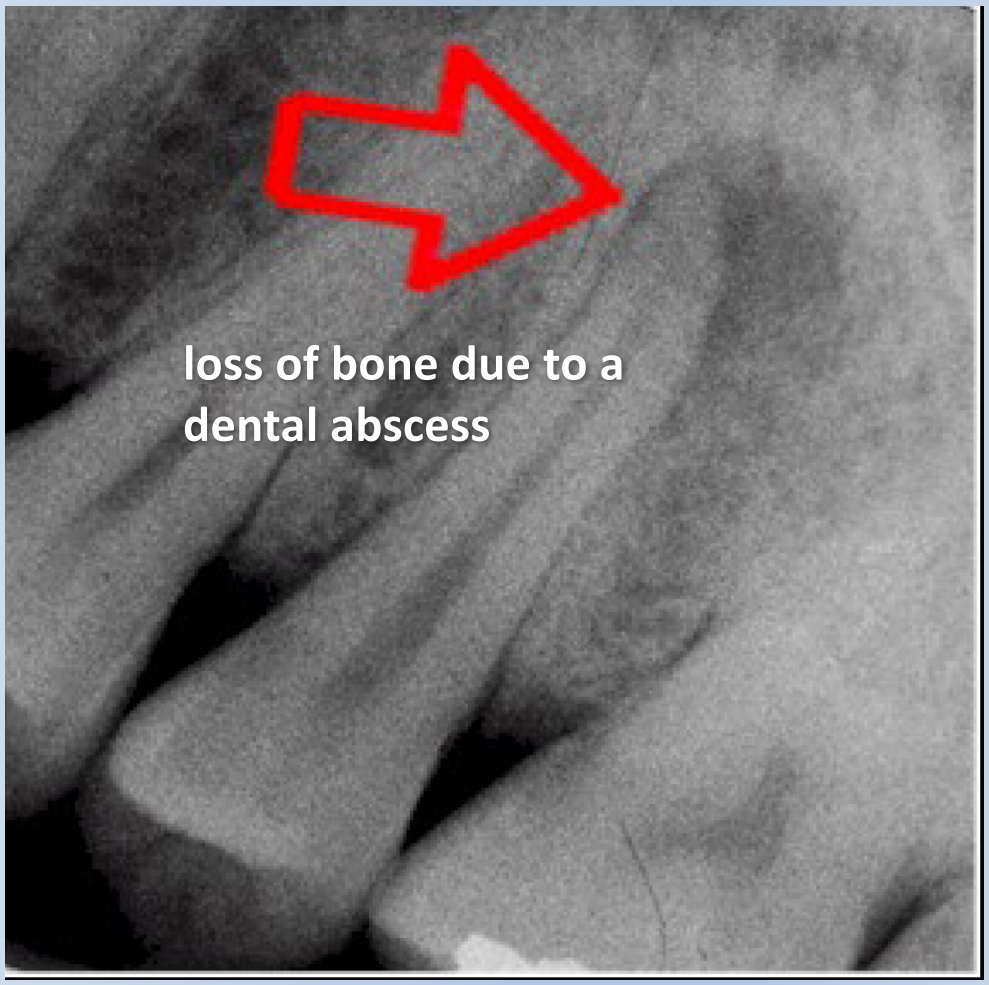
Normal



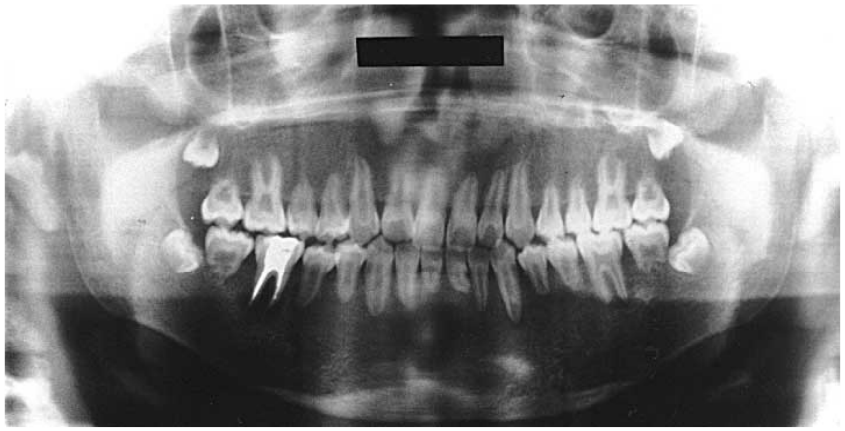
XLH



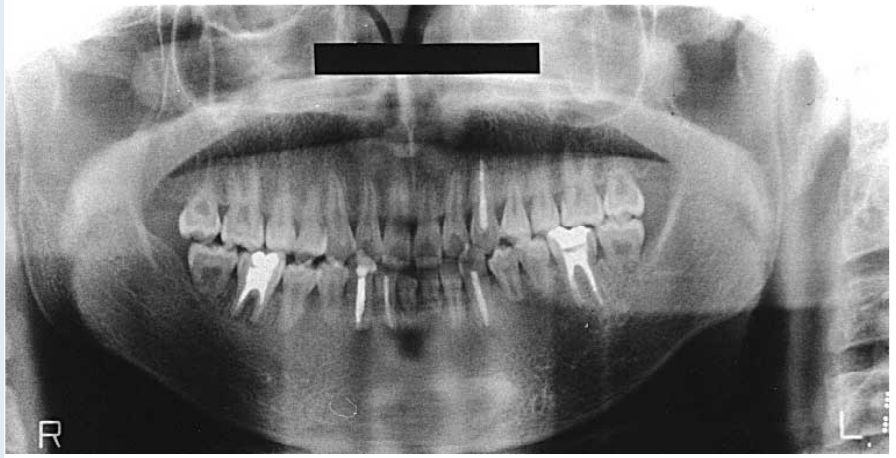
XLH



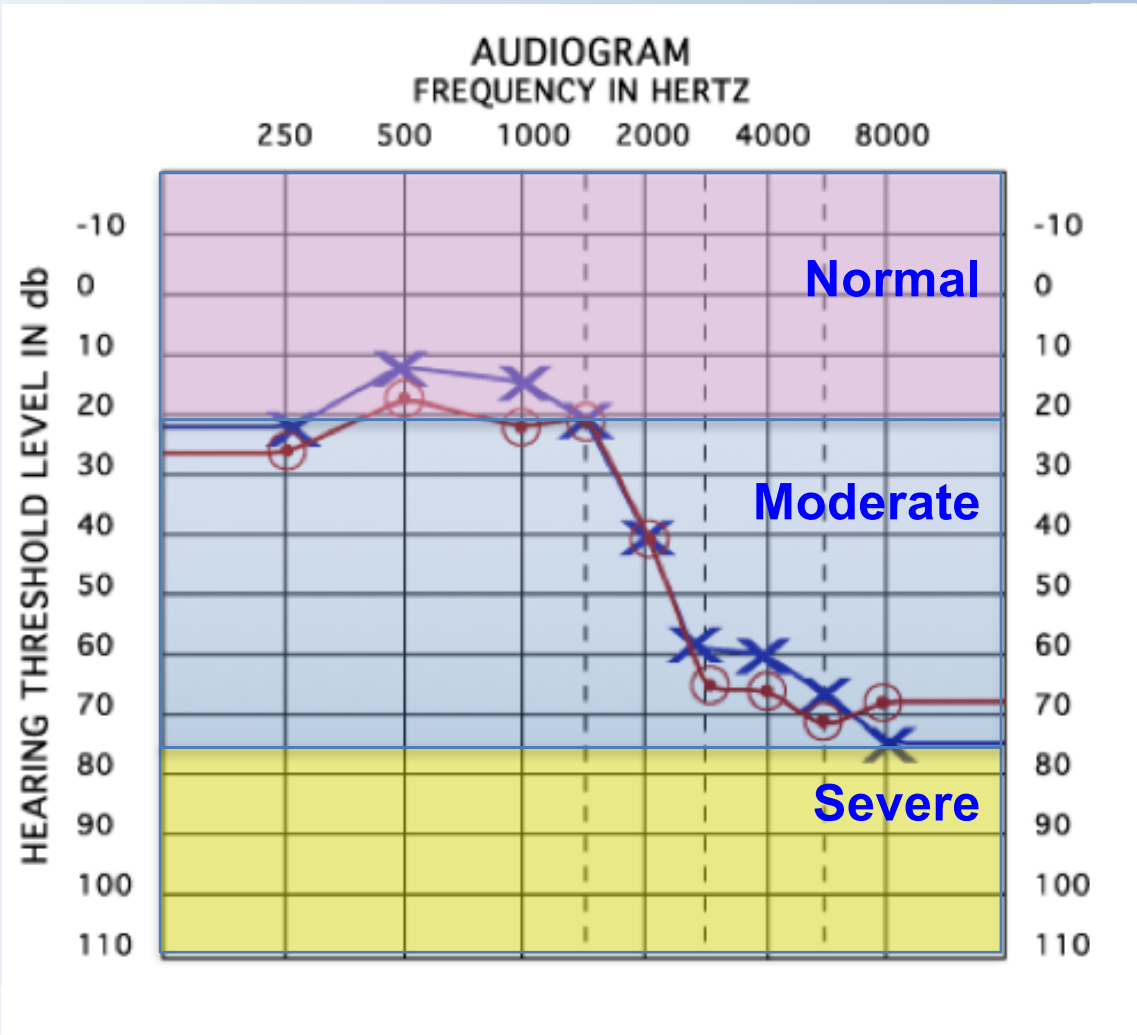
Dental disease with abscesses (age 15, top; age 23, bottom)



6. Panoramic radiograph (after endodontic therapy of right mandibular first molar at 15 years). Root plasia (short root tooth) was observed bilaterally in maxillary and mandibular first premolars, second nolars, second molars, and bilateral mandibular central incisors, but degree was slight in right mandibular premolar. Trabecular structure was abnormal.

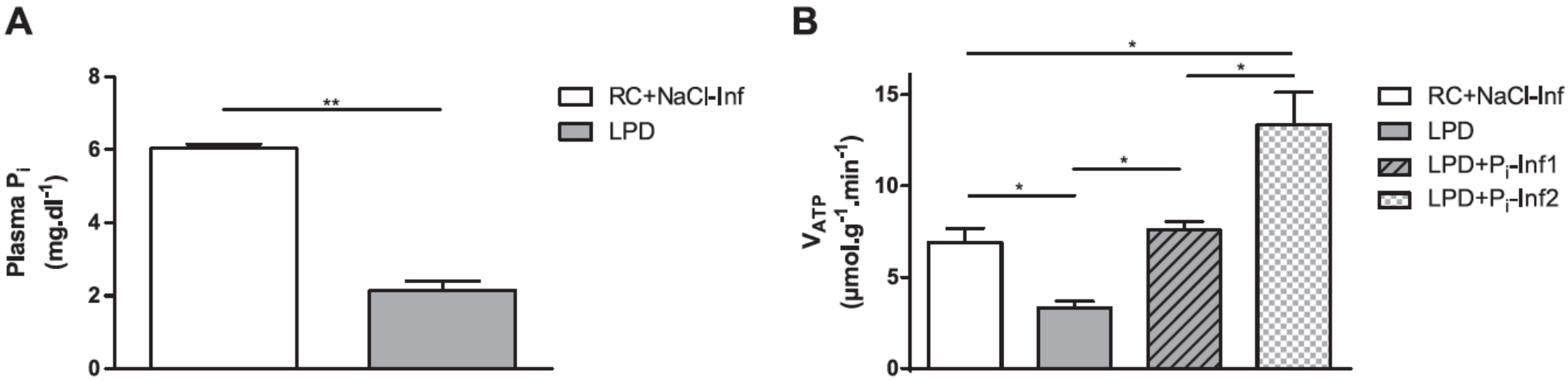


Complications of XLH in adults: Hearing loss



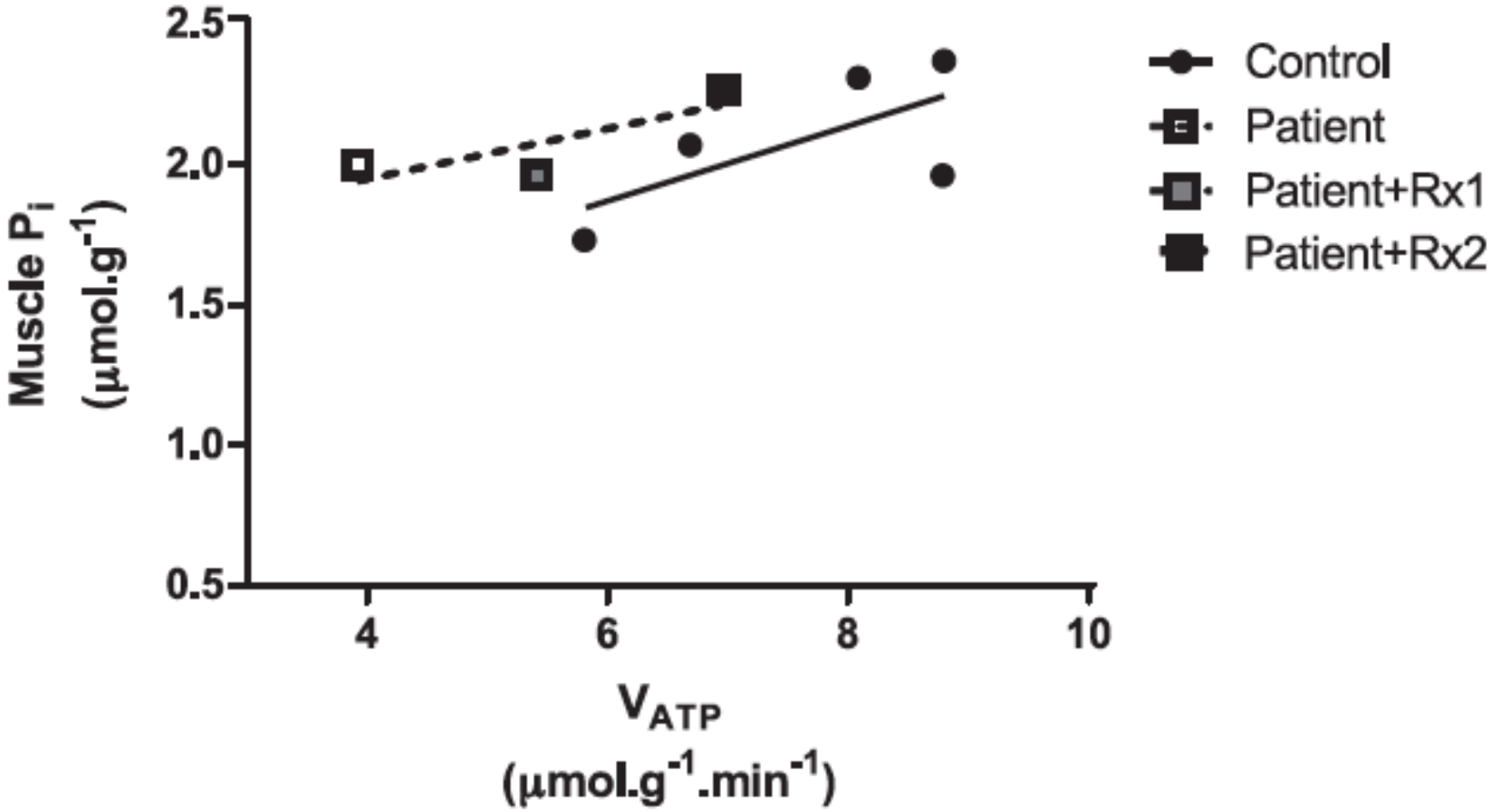
Complications of XLH in adults: A sense of muscle weakness and early fatigability

- This may be related to a reduction in muscle ATP synthesis



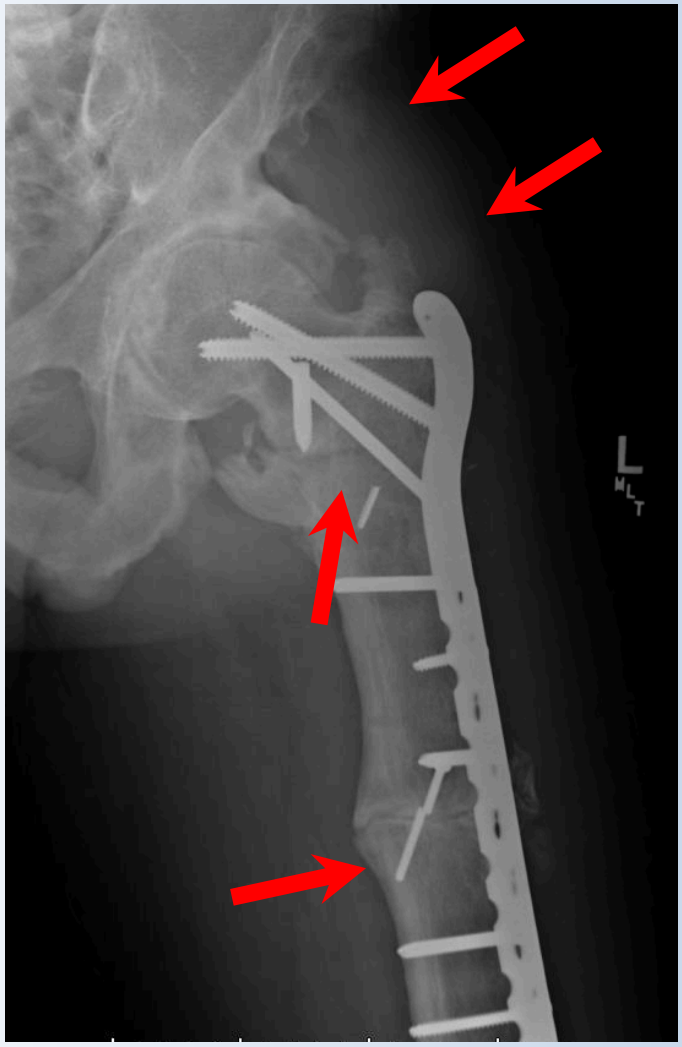
FASEB J. 2016 Jun 23. pii: fj.201600473R. [Epub ahead of print]

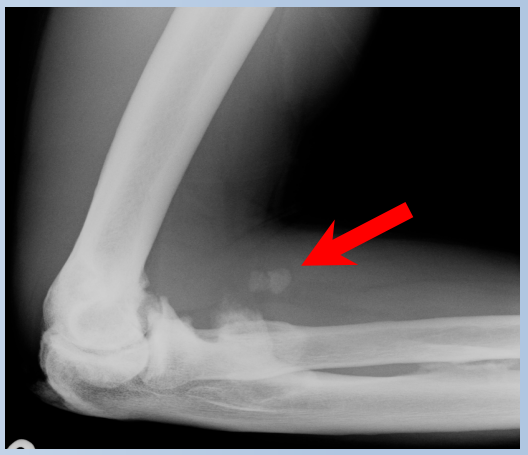
In a hypophosphatemic patient (with HHRH) correcting the hypophosphatemia improves rates of muscle ATP synthesis

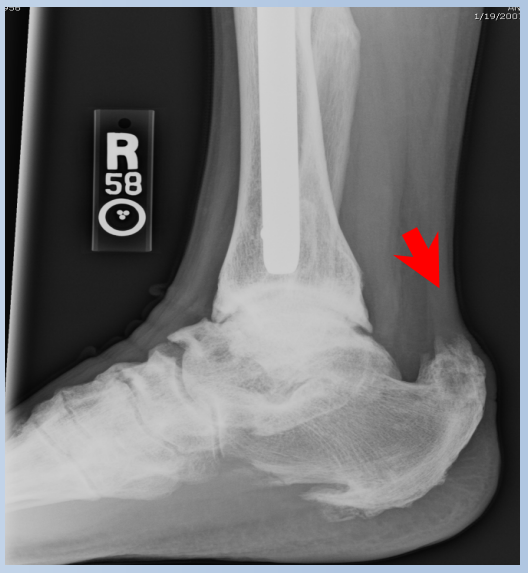


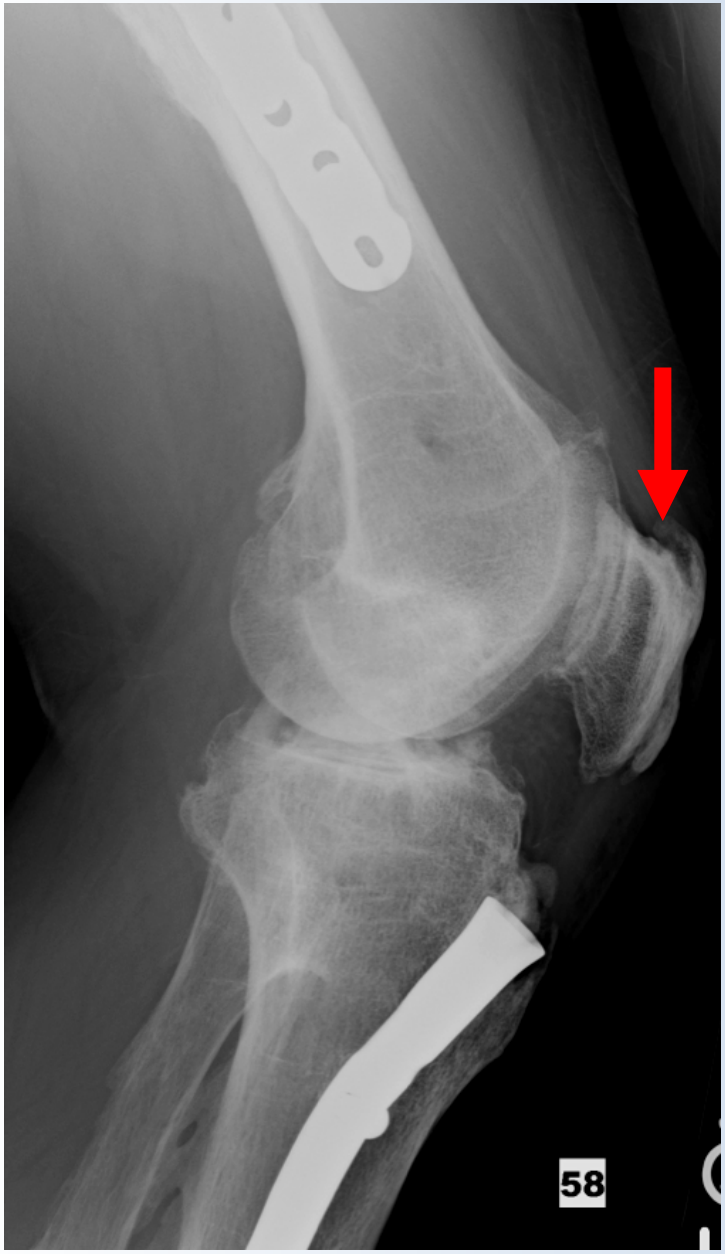
FASEB J. 2016 Jun 23. pii: fj.201600473R. [Epub ahead of print]

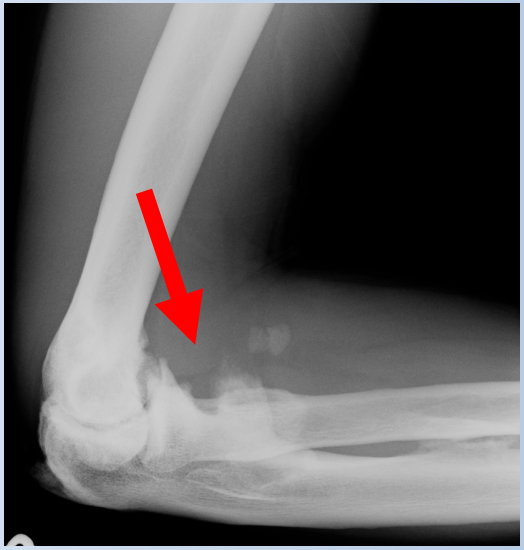
Complications of XLH in Adults: Fractures and Enthesopathy

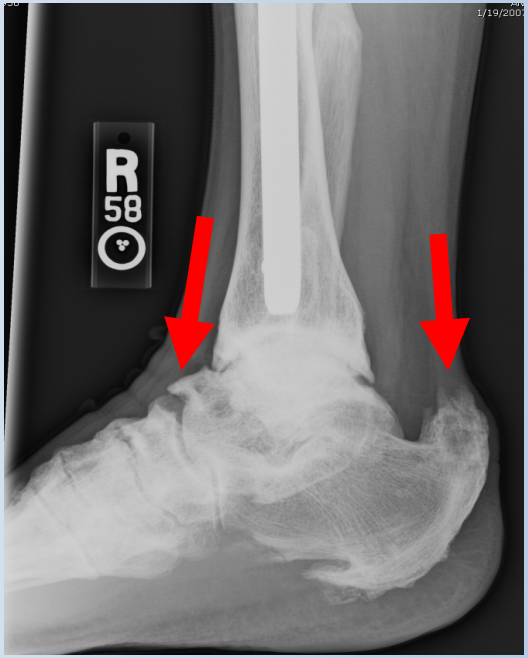










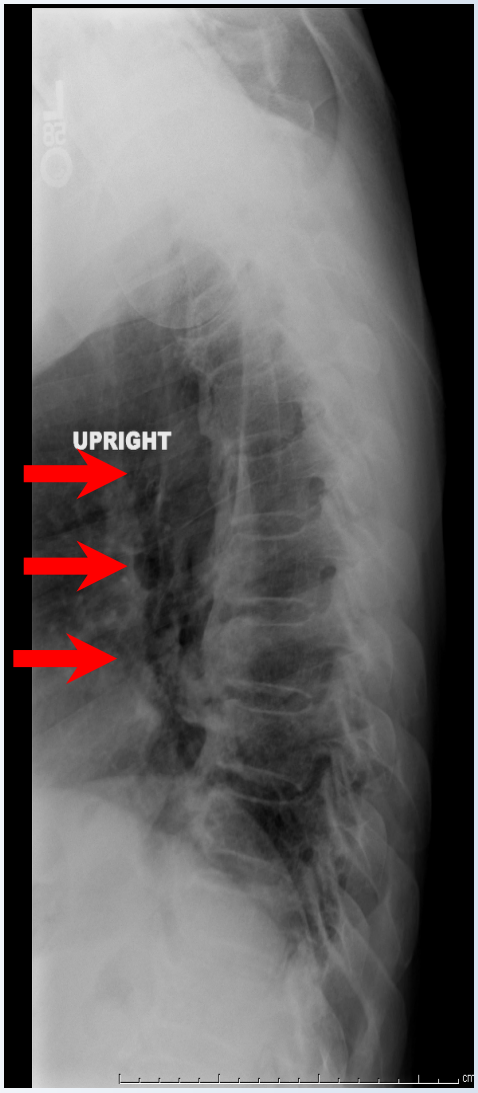


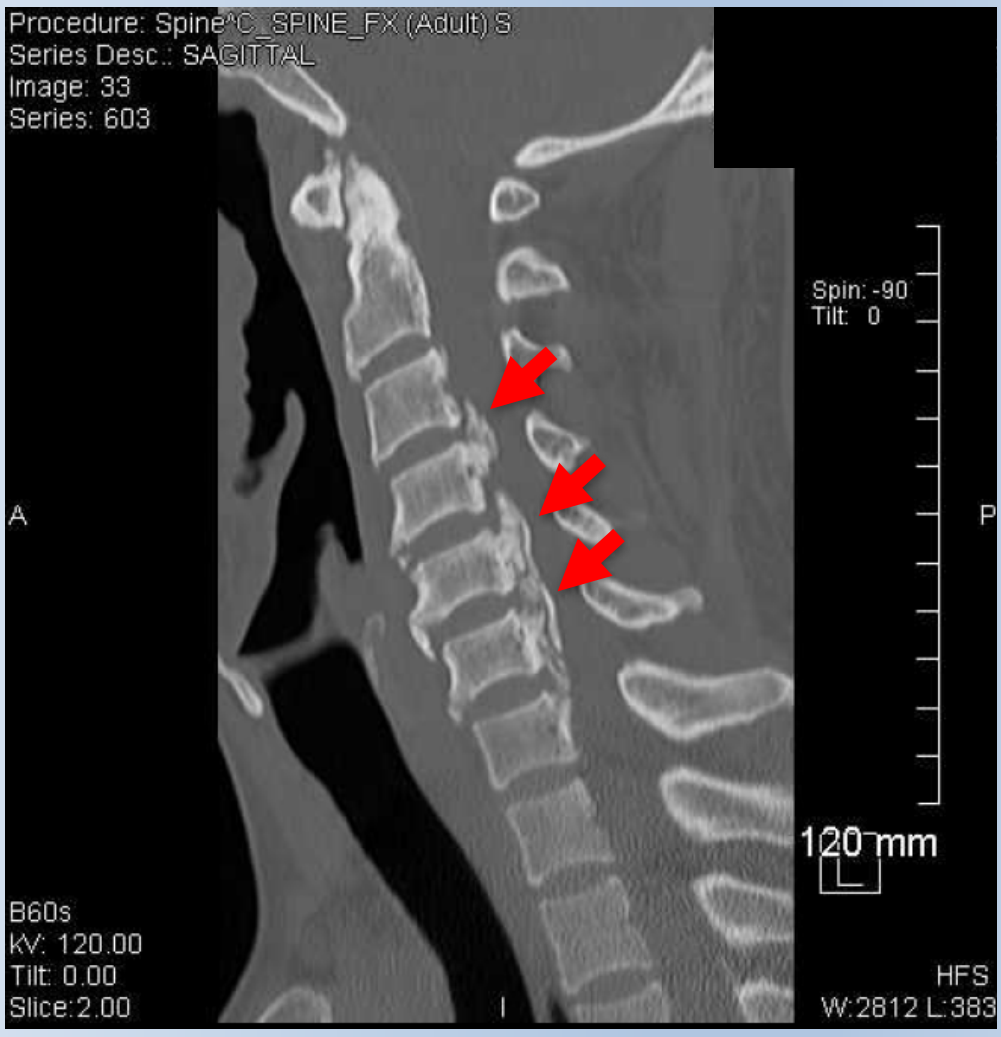
Osteophytes and Calcified Entheses

ale Bone Center

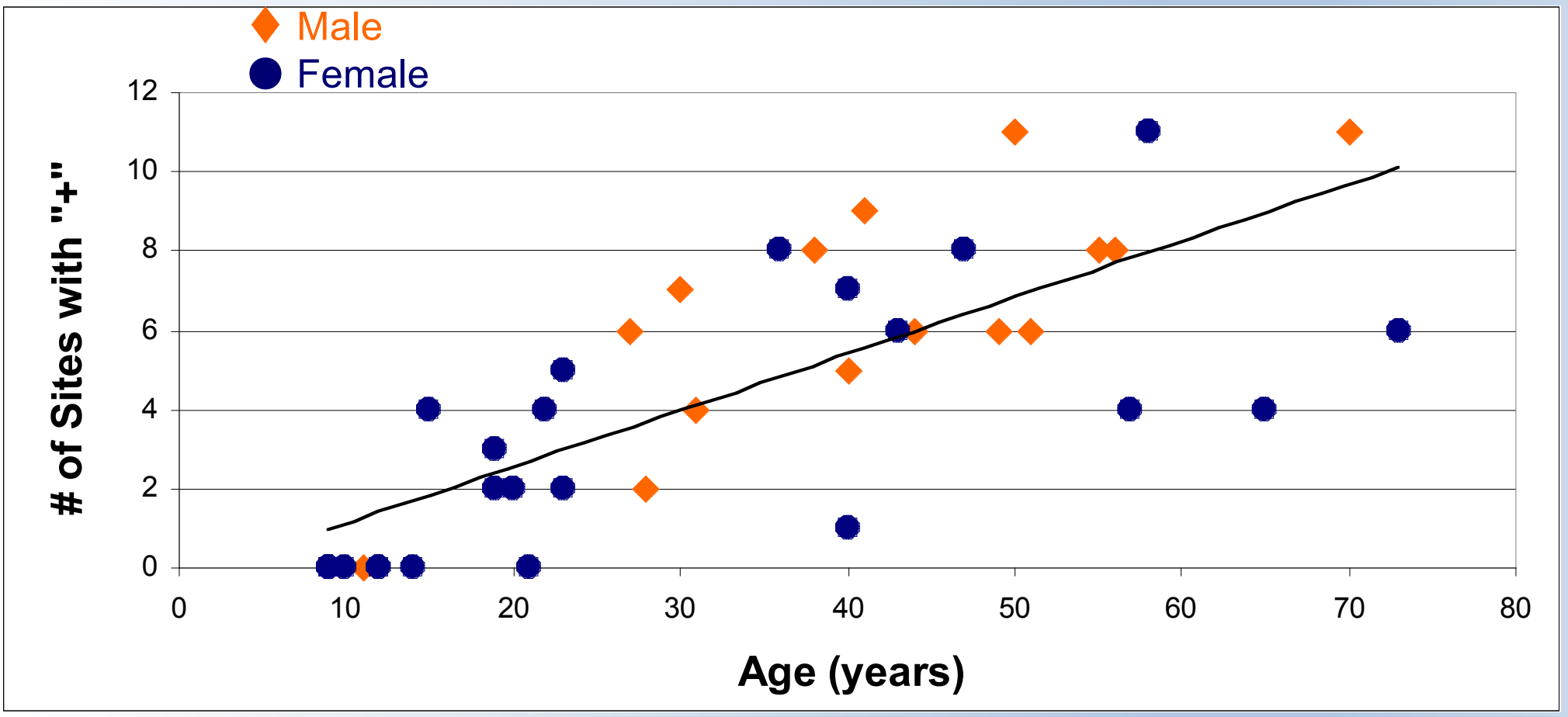
ASBMR

Complications of XLH in Adults: Spinal Ligament Calcification



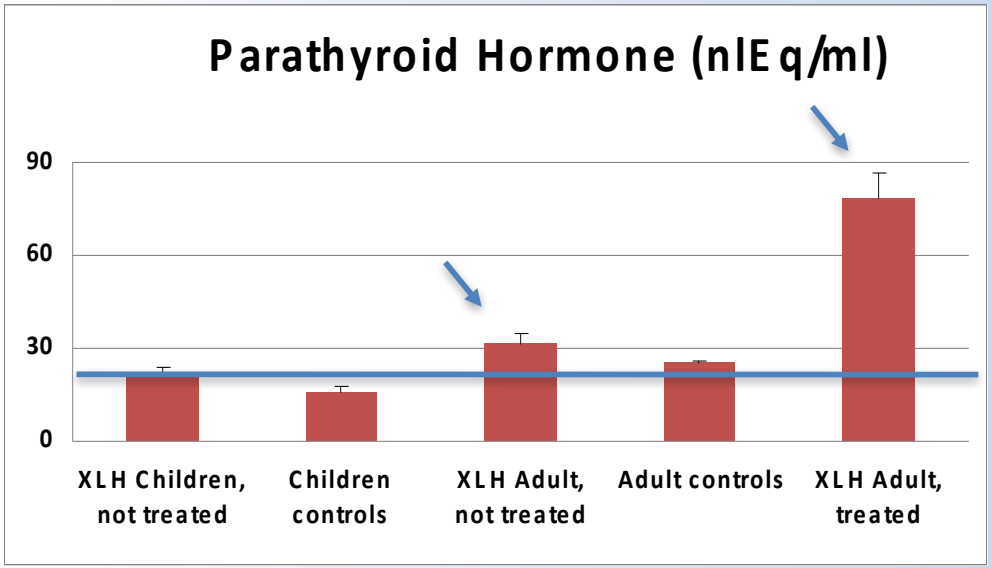


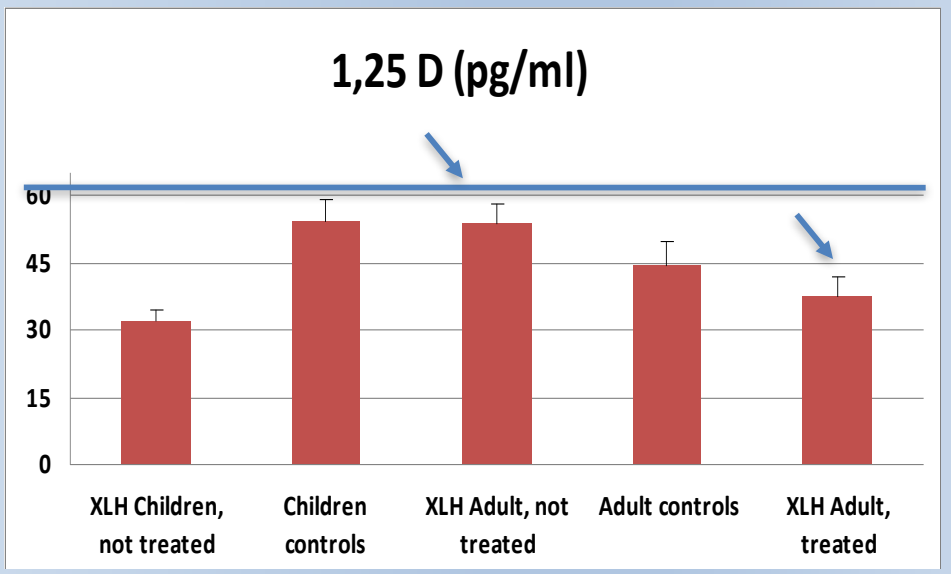
Enthesopathy: Sites vs. Age

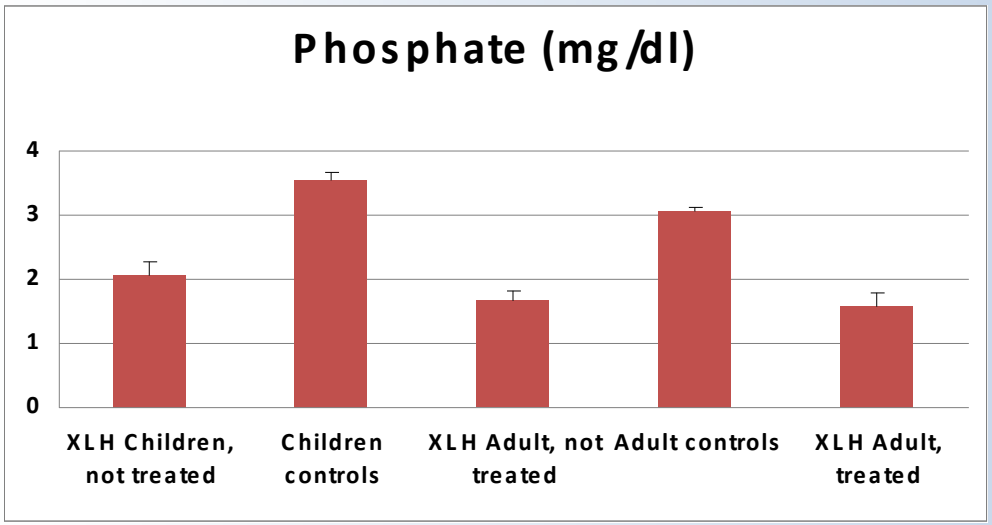


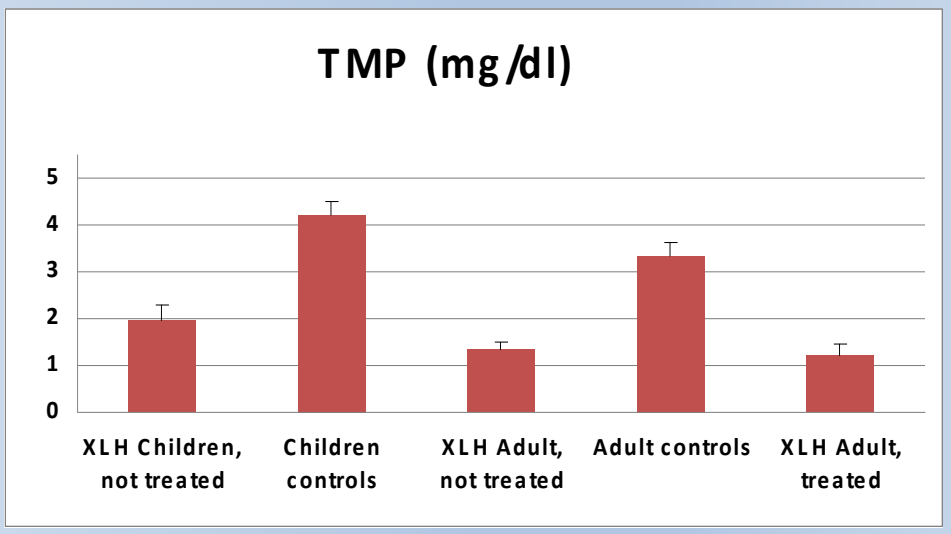
JCEM 95:E352, 2010

Biochemistry in XLH, by Age and Disease









JCEM 95:E352, 2010

ale Bone Center

ASBMR

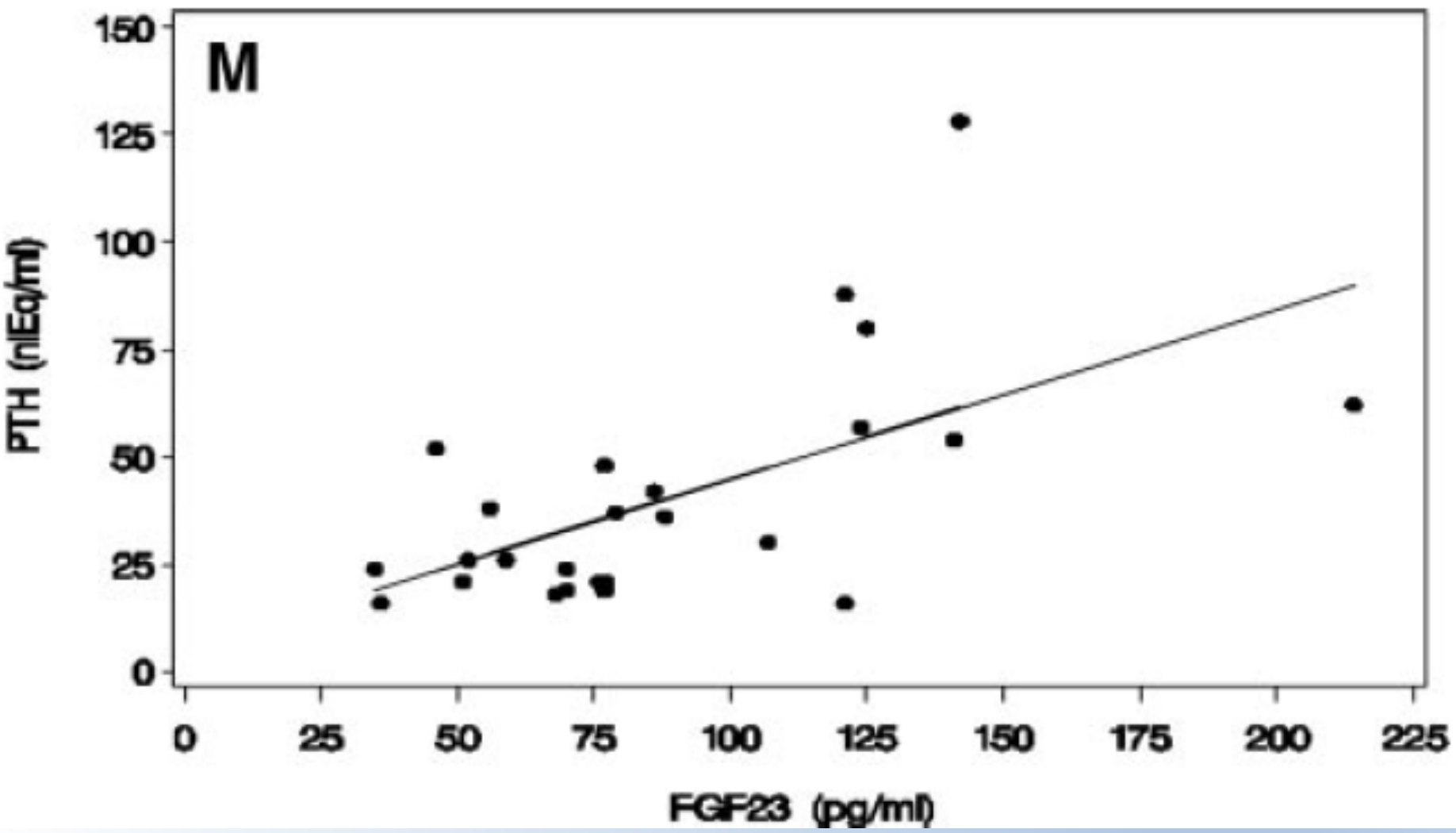
XLH Subjects: Correlates of Biochemical Variables

klotho	*FGF23*	*P*	*PTH*	*1,25D*	*TMP*
Correlation Coefficient (Pearson)	0.030	0.091	-0.267	-0.377	0.166
P value	0.888	0.653	0.178	**0.053**	0.407

FGF23	*klotho*	*P*	*PTH*	*1,25D*	*TMP*
Correlation Coefficient (Pearson)	0.030	-0.259	0.602	-0.339	-0.271
P value	0.888	0.211	**0.002**	0.097	0.190

JCEM 95:E352, 2010

FGF23 levels correlate with circulating levels of PTH in XLH



JCEM 95:E352, 2010

Current approaches to treating adult patients with XLH

Non-Pharmacologic Recommendations

- Nutritional counseling
- Regular aerobic exercise
- Meticulous dental hygiene
- Regular auditory examinations

We undertook a prospective trial of therapy in adults with XLH

0021-972X/92/7503-0879$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 75, No. 3
Printed in U.S.A.

A Prospective Trial of Phosphate and 1,25-Dihydroxyvitamin D_3 Therapy in Symptomatic Adults with X-Linked Hypophosphatemic Rickets*

WILLIAM SULLIVAN, THOMAS CARPENTER, FRANCIS GLORIEUX, ROSE TRAVERS, AND KARL INSOGNA

Endocrine Division, Departments of Medicine and Pediatrics, Yale University School of Medicine (W.S., T.C., K.I.), New Haven, Connecticut 06510–8056; and the Genetics Unit, Shriners Hospital, McGill University (F.G., R.T.), Montreal, Quebec, Canada

ale Bone Center

ASBMR

Characteristics of the 18 adult study subjects

TABLE 1. Clinical characteristics and prior treatment history in 18 patients with XLH

Subject no.	Sex	Age (yr)	Family history				Treatment history [ages (yr) when treated]	
			Age at diagnosis (yr)	Affected parent	Offspring	Osteotomy	Vitamin D_2	Phosphate
1	M	33	0.3	+	+	+	[a]	1–18
2	M	36	1.9	+	+	−	2–18	6–18
3	M	34	0.3	+	+	−	7–17	5–17
4	F	31	[a]	+	−	+	16	
5	F	41	26	+	−	+	12–36	
6	F	65	50	−	+	−		
7	M	23	0.7	+	−	−	1–16	1–16
8	M	32	10	+	+	−	10–21	10–21
9	M	33	[a]	+	+	+	[a]	[a]
10	F	26	15	−	+	+	[a]	[a]
11	M	43	[a]	−	−	+	[a]	[a]
12	M	47	[a]	+	+	+	[a]	[a]
13	F	47	23	−	+	+		
14	F	47	7	−	+	−	7–19	7–19
15	F	20	2	+	−	−	2–10	3–15
16	F	17	1.5	−	−	+	2–12	3–12
17	F	59	7	−	+	+		7–12
18	M	31	3	−	−	−	3–19	3–19

Family history: +, affected; −, unaffected. Osteotomy: +, history of in the past.
[a] Received treatment in childhood; further details unknown.

Pre-treatment Biochemical Data

TABLE 3. Biochemical data before treatment as an adult

Subject no.	sPO_4 (1.00–1.45 mmol/L)	sCa (2.27–2.64 mmol/L)	sCr (44–106 pmol/L)	Alkaline phosphatase (0.5–1.9 μkat/L)	PTH (<25 nLeq/mL)	TMP/GFR (0.80–1.35 mmol/L)	25OHD (25–150 nmol/L)	$1,25\text{-}(OH)_2D$ (48–155 pmol/L)	uCa (<6.2 mmol/day)
1	0.48	2.27	71	0.85	60[a]	0.50		73.2	3.24
2	0.55	2.22	62	0.75	12	0.53		86.4	3.07
3	0.65	2.30	44	1.67	21	0.52	28.2	91.4	2.40
4	0.65	2.17	53	1.08	53	0.48	45.7	83.7	0.34
5	0.77	2.24	62	0.83	31	0.51	579.0	57.1	5.04
6	0.65	2.22	62	1.12	35	0.48	51.9	97	2.69
7	0.65	2.35	88	1.10	15	0.57	44.2	73	3.39
8	0.65	2.42	53	1.22		0.61		113	2.40
9	0.55	2.49	62	2.03	41	0.49	72.9	118	0.80
10	0.58	2.30	71	0.58	56	0.45	65.6	40.8	
11	0.42	2.27	97	2.77	77[a]	0.58		43.2	1.60
12	0.55	2.24	80	1.00			57.2	92.6	2.74
13	0.71	2.37	53	0.87					0.36
14	0.61	2.27	62	0.82			79.9	97.2	
15	0.87	2.47	80	1.77	11	0.61	64.9	68.2	3.84
16	0.84	2.52	53	1.42	66	0.70	39.4	138.7	0.36
17	0.77	2.52	80	0.68	61				
18	0.55	2.32	80	2.28	44	0.35	45.2	90	3.99
Mean	0.61	2.31	67	1.26	30	0.53	57	83	2.45
SEM	0.03	0.03	4	0.16	6	0.02	6	6	0.38

Subject 5 had been treated with vitamin D (50,000 U/day) before being placed on phosphate and calcitriol treatment (excluded from mean). Subject 16 had been on continuous treatment since childhood (excluded from mean). Subjects 17 and 18 were treated in childhood, but not as adults (excluded from mean). s, Serum; u, urinary.

[a] PTH by commercial assay (normal, 60–100; excluded from mean).

Pre-treatment Histomorphometry

TABLE 4. Pretreatment histomorphometry

Patient no.	BV/TV (%)	BS/TV (mm^2/mm^3)	TbTh (μm)	OV/TV (%)	OV/BV (%)	OS/BS (%)	OTh (μm)	ObS/BS (%)	OcS/BS (%)	Oc/mm^2 TA no.
7	56.8	4.0	362	10.6	18.7	64.4	45.1	10.0	2.7	2.90
8	31.2	3.0	261	11.5	36.9	88.0	49.6	5.0	1.4	1.02
10	28.5	3.4	213	5.9	20.6	76.6	26.7	8.2	1.7	1.51
11	32.7	3.0	275	11.4	35.0	89.9	51.6	4.2	1.0	0.56
12	34.7	4.9	179	1.3	3.9	32.2	10.6	13.4	2.0	2.2
13	24.9	3.2	196	4.8	19.1	71.4	25.0	8.8	0.9	0.80
14	42.0	3.8	278	7.5	17.9	79.6	27.5	3.5	0.8	1.01
15	32.0	2.5	321	0.3	1.0	14.2	10.9			
Mean	35.4	3.5	261	6.7	19.1	64.5	30.9	7.6	1.5	1.4
SEM	3.5	0.2	22	1.6	4.5	9.6	5.8	1.4	0.3	0.3
Normal*										
Mean	28.3	3.9	186	0.4	1.6	16.0	8.7	5.4	1.0	0.9
SEM	1.2	0.1	7	0.03	0.2	1.2	0.4	0.6	0.1	0.1

BV/TV, bone volume (trabecular) as % of total section; BS/TV, bone surface per total volume; TbTh, trabecular thickness; OV/TV, osteoid volume as % of total section; OV/BV, osteoid volume as % of bone volume; OS/BS, total osteoid surface; OTh, osteoid thickness; ObS/BS, osteoblast surface; OcS/BS, osteoclast surface; Oc/mm^2 TA, osteoclast number.

[a] The normative data are unpublished results of 16 biopsy specimens from 9 women and 7 men with an age range of 17–23 yr (Glorieux, F., R. Travers, A. Taylor, and M. Norman).

Mean doses of phosphate and calcitriol used in the study

Subject no.	Ages when treated (yr)	Medication dosages: Phosphate (g/day) Initial	Phosphate (g/day) Range	1,25-$(OH)_2D$ (μg/day) Initial	1,25-$(OH)_2D$ (μg/day) Range
1	24–33	1.25	0.75–1.25	1.0	0.5–1.0
2	30–36	1.25	1.0–1.25	1.0	1.0–2.0
3	33–34	1.5	1.5	0.50	0.50–0.75
4	25–27	1.0	1.0–1.25	0.75	0.75–1.5
5	36–38	1.0	1.0	0.50	0.50
6	60–62	1.0	1.0	0.50	0.50–0.75
7	17–23	1.25	1.25–2.5	1.5	0.5–1.5
8	30–32[a]	1.5	1.5–2.5	1.0	1.0–2.0
9	32–33			0.5	0.5
10	25–26	1.0	1.0–1.25	1.0	1.0–2.0
11	32–35[b]	2.0	2.0–3.0	1.0	1.0–3.0
12	38–40	1.5	1.5–2.0	1.0	1.0–1.25
13	38–47	2.0	1.5–2.5	0.75	0.75–2.5
14	38–47	0.5	0.5	0.5	0.5
15	16–21	0.5	0.5–2.0	0.5	0.5 1.0
16	16–17	1.0	1.0	0.5	0.5–1.0
Mean		1.22		0.78	
SEM		0.11		0.08	

Subjects 17 and 18 were treated in childhood, but not as adults.
[a] Subject 8 was also treated at ages 23–25 and 26–27 yr.
[b] Subject 11 received 1,25-$(OH)_3D_3$ alone from age 37–40 yr.

Biochemical Response to Treatment

TABLE 5. Biochemical response to phosphate/calcitriol treatment

Subject no.	sPO$_4$		sCa		uCa		sCr		Alkaline phosphatase	
	Mean[a]	Δ[b]	Mean[a]	Δ[b]	Mean[a]	Δ[b]	Mean[a]	Δ[b]	Mean[a]	Δ[b]
1	0.74	+0.26	2.38	+0.11	4.14	+0.90	68	−2	0.71	−0.14
2	0.61	+0.06	2.37	+0.15	7.25	+4.18	55	−6	0.62	−0.13
3	0.76	+0.11	2.44	+0.14	3.36	+0.96	53	+10	1.46	−0.21
4	0.68	+0.03	2.18	+0.01	5.59	+5.24	53	0	0.77	−0.31
5	0.63	−0.13	2.35	+0.11	6.68	+1.64	53	−8	0.72	−0.11
6	0.70	−0.05	2.24	+0.02	4.22	+1.53	57	−4	0.93	−0.19
7	1.27	+0.62	2.49	+0.14	4.94	+1.55	87	−1	1.22	+0.12
8	0.74	+0.09	2.39	−0.03	4.32	+1.92	62	+9	1.87	+0.65
9	0.77	+0.22	2.32	−0.17	2.92	+2.12	62	0	2.30	+0.27
10	0.71	+0.13	2.22	−0.08			57	−13	1.10	+0.52
11	0.80	+0.38	2.55	+0.28	3.26	+1.66	140	+43	1.22	−1.55
12	0.76	+0.21	2.26	+0.02	5.94	+3.20	81	+1	0.90	−0.10
13	0.79	+0.08	2.31	−0.05	5.13	+4.77	58	+5	0.66	−0.21
14	0.68	+0.07	2.30	+0.03	4.75		61	−1	0.54	−0.28
15	0.78	−0.09	2.32	−0.15	1.59		83	+3	1.62	−0.15
16	0.88	+0.04	2.45	−0.07	0.60	+0.24	65	+12	1.67	+0.25
Mean	0.77	+0.13	2.34	+0.04	4.39	+2.47	69	+3	1.14	−0.12
SEM	0.04[c]	0.05	0.03	0.03	0.44[c]	0.43	6	1	0.14	0.13

s, Serum; u, urinary.

[a] Values shown are the means of 2–14 determinations/subject during the treatment period. Subjects 5 (on vitamin D at baseline evaluation) and 16 (on continuous treatment since childhood) were excluded from mean.

[b] Differences between mean values from the pretreatment (Table 3) and treatment periods.

[c] Significantly different from pretreatment value ($P < 0.015$). For pretreatment values, see Table 3.

Biochemical Response to Treatment

TABLE 6. Serum vitamin D metabolites and iPTH

	25OHD (nmol/L)	1,25-$(OH)_2$D (pmol/L)	iPTH (nLeq/mL)
Pretreatment	57 ± 6 (8)	86 ± 7 (11)	30 ± 6 (8)
During treatment	61 ± 7 (8)*	87 ± 6 (11)*	38 ± 7 (8)*
Normal range	25–100	48–156	<25

The number of subjects is given in parentheses.
* P = NS, pretreatment *vs.* during treatment.

Histomorphometric Response to Conventional Treatment with Calcitriol and Pi

TABLE 7. Treatment histomorphometry as percentage of pretreatment values

Patient no.	BV/TV	BS/TV	TbTh	OV/TV	OV/BV	OS/BS	OTh	ObS/BS	OcS/BS	Oc/mm² TA
7	66.6	105.8	63	30.4	45.6	69.0	44.9	18.2	54.4	54.5
8	93.4	161.3	58	75.0	80.4	102.3	49.5	67.5	47.2	78.4
10	109.8	125.6	88	104.6	95.2	115.3	74.7	42.9	13.6	12.6
11	122.8	99.7	123	27.7	22.6	67.4	39.5	201.9	257.4	362.5
13	146.7	102.8	143	9.9	6.7	20.9	46.6	47.3	63.2	50.0
14	58.8	96.1	61	29.3	49.8	48.7	61.4			
Mean	99.7	5.2	89	46.1	50.1	70.6	52.8	75.6	87.2	111.6
SEM	12.5	9.3	13	13.4	12.5	12.9	4.8	29.1	38.8	56.9
P				<0.02	<0.02		<0.0005			

For key to abbreviations, see legend to Table 4.

1. Conventional treatment does not affect enthesopathy
2. Male sex and obesity portend worse enthesopathy
3. Hyperparathyroidism is a/w worse enthesopathy

Table 3. Age-Adjusted and Multivariate-Adjusted Multiple Linear Regression Models of the Relationship Between Proportion of Adult Life With Treatment, Other Predictors, and Number of Sites of Enthesopathy

	Age-Adjusted R^2 = 0.38		Multivariate-Adjusted R^2 = 0.63	
Characteristic	**β (SE)**	***P* Value**	**β (SE)**	***P* Value**
Proportion of adult life with treatment				
0	0.071 (0.27)	.80	−0.092 (0.23)	.69
0 < x < 1	0.0040 (0.19)	.99	−0.0 000 015 (0.17)	1.0
1	Reference		Reference	
Global *P* value		.96		.90
P value for trend		.68		.50
Age, y	0.033 (0.010)	<.0010	0.023 (0.006)	<.0010
Sex				
Male			Reference	
Female			−0.42 (0.16)	.0080
BMI, kg/m^2			0.034 (0.0090)	<.0010
Mutation severity[a]				
Not severe			Reference	
Severe			0.14 (0.18)	.42
PTHauc[b]			0.00 028 (0.00 014)	.051
Proportion of treatment in childhood				
<0.80			0.30 (0.18)	.10
≥0.80			Reference	

[a] Mutation analyses from five subjects were either not performed or not definitive and were included in a "missing category."

JCEM 100:3625, 2015

ale Bone Center

ASBMR

Conventional treatment does seem to ameliorate dental disease in adults with XLH

Table 5. Age-Adjusted and Multivariate-Adjusted Multiple Logistic Regression Models of the Relationship Between Proportion of Adult Life With Treatment, Other Predictors, and Severity of Dental Disease

	Age-Adjusted R^2 = 0.25		Multivariate-Adjusted R^2 = 0.44	
Characteristic	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Proportion of adult life with treatment				
0	7.8 (0.85–71)	.069	25 (1.2–520)	.038
0 < x < 1	2.3 (0.51–11)	.27	7.1 (0.88–58)	.067
1	1.0		1.0	
Global *P* value		.038		.0080
P value for trend		.20		.066
Age, y	1.1 (1.0–1.2)	.0030	1.1 (1.0–1.2)	.019
Sex				
Male			1.0	
Female			0.15 (0.020–1.1)	.061
Mutation severity[a]				
Not severe			1.0	
Severe			3.9 (0.63–25)	.14
Proportion of treatment in childhood				
<0.80			7.2 (0.71–73)	.10
≥0.80			1.0	

[a] Mutation analyses from five subjects were either not performed or not definitive and were included in a "missing category."

JCEM 100:3625, 2015

Conventional treatment does seem to ameliorate dental disease in adults with XLH

Table 6. Age-Adjusted and Multivariate-Adjusted Multiple Linear Regression Models of the Relationship Between Proportion of Total Life With Treatment, Other Predictors, and Severity of Dental Disease

	Age-Adjusted R^2 = 0.28		Multivariate-Adjusted R^2 = 0.44	
Characteristic	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Proportion of total life with treatment				
0–0.435	8.8 (1.1–70)	.040	31 (2.2–450)	.012
0.436–0.587	5.6 (0.84–38)	.075	25 (1.8–340)	.017
0.588–0.880	2.0 (0.33–12)	.45	4.8 (0.49–51)	.20
0.881–1.0	1.0		1.0	
Global *P* value		.012		.0010
P value for trend		.046		.015
Age, y	1.1 (1.0–1.1)	<.0010	1.1 (1.0–1.2)	.010
Sex				
Male			1.0	
Female			0.080 (0.0090–0.71)	.023
Mutation severity[a]				
Not severe			1.0	
Severe			5.2 (0.82–33)	.080

[a] Mutation analyses from five subjects were either not performed or not definitive and were included in a "missing category."

JCEM 100:3625, 2015

The hyperparathyroidism that so frequently complicates XLH has become an increasing concern for our group

- Based on the data I just presented suggesting an association of hyperparathyroidism with the extent of enthesopathy, the association of PTH with higher circulating levels of FGF23 as well as the data from three other studies we have undertaken:

Nocturnal Hyperparathyroidism: A Frequent Feature of X-Linked Hypophosphatemia*

T. O. CARPENTER, M. A. MITNICK, A. ELLISON, C. SMITH, AND K. L. INSOGNA

JCEM 78:1378, 1994

24,25 Dihydroxyvitamin D Supplementation Corrects Hyperparathyroidism and Improves Skeletal Abnormalities in X-Linked Hypophosphatemic Rickets—A Clinical Research Center Study*

THOMAS O. CARPENTER, MARC KELLER, DANA SCHWARTZ, MARYANN MITNICK, CYNTHIA SMITH, ALICE ELLISON, DENNIS CAREY, FLORENCE COMITE, RONALD HORST, ROSE TRAVERS, FRANCIS H. GLORIEUX, CAREN M. GUNDBERG, A. ROBIN POOLE, AND KARL L. INSOGNA

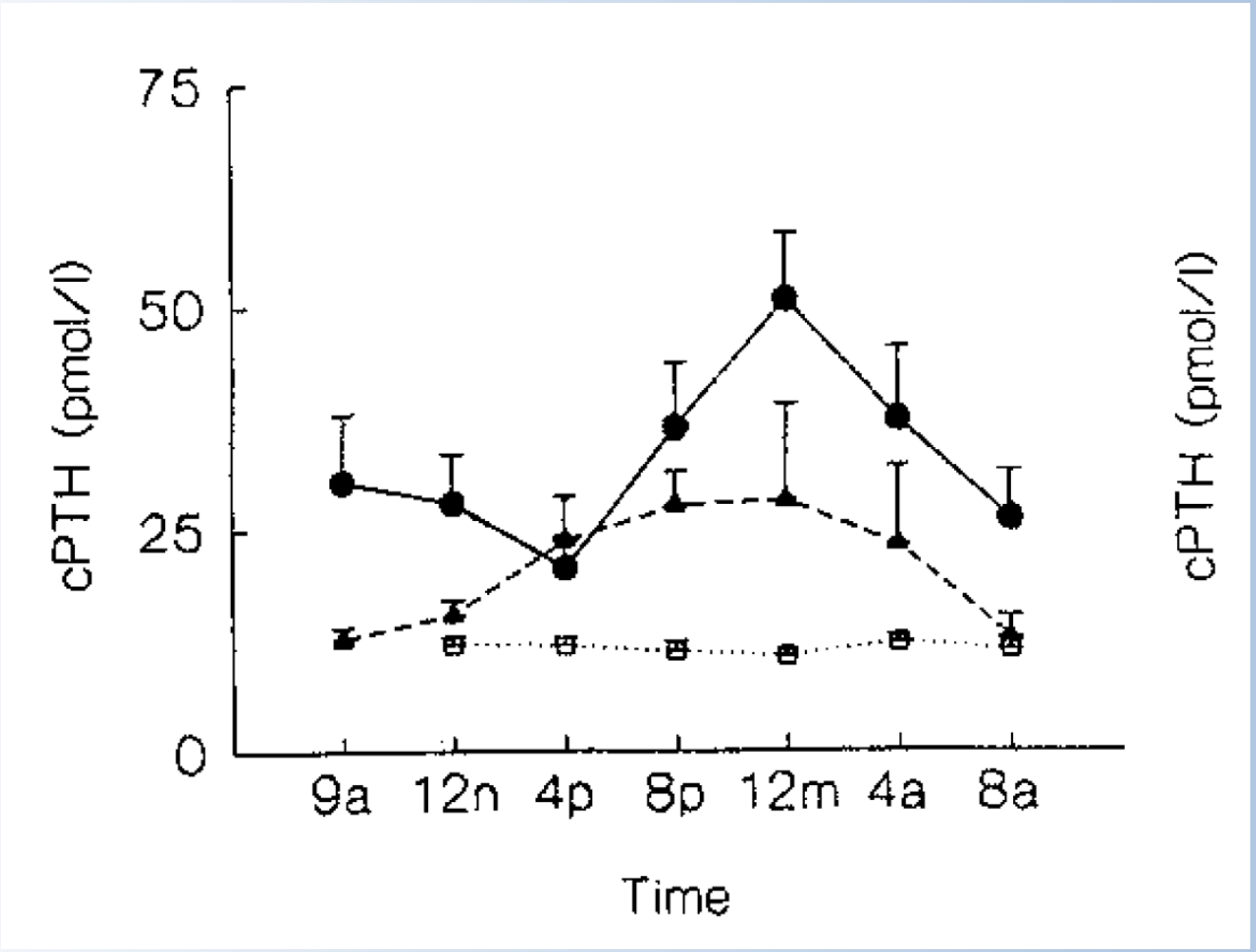
JCEM 81:2318, 1996

Effect of Paricalcitol on Circulating Parathyroid Hormone in X-Linked Hypophosphatemia: A Randomized, Double-Blind, Placebo-Controlled Study

Thomas O. Carpenter, Elizabeth A. Olear, Jane H. Zhang, Bruce K. Ellis, Christine A. Simpson, David Cheng, Caren M. Gundberg, and Karl L. Insogna

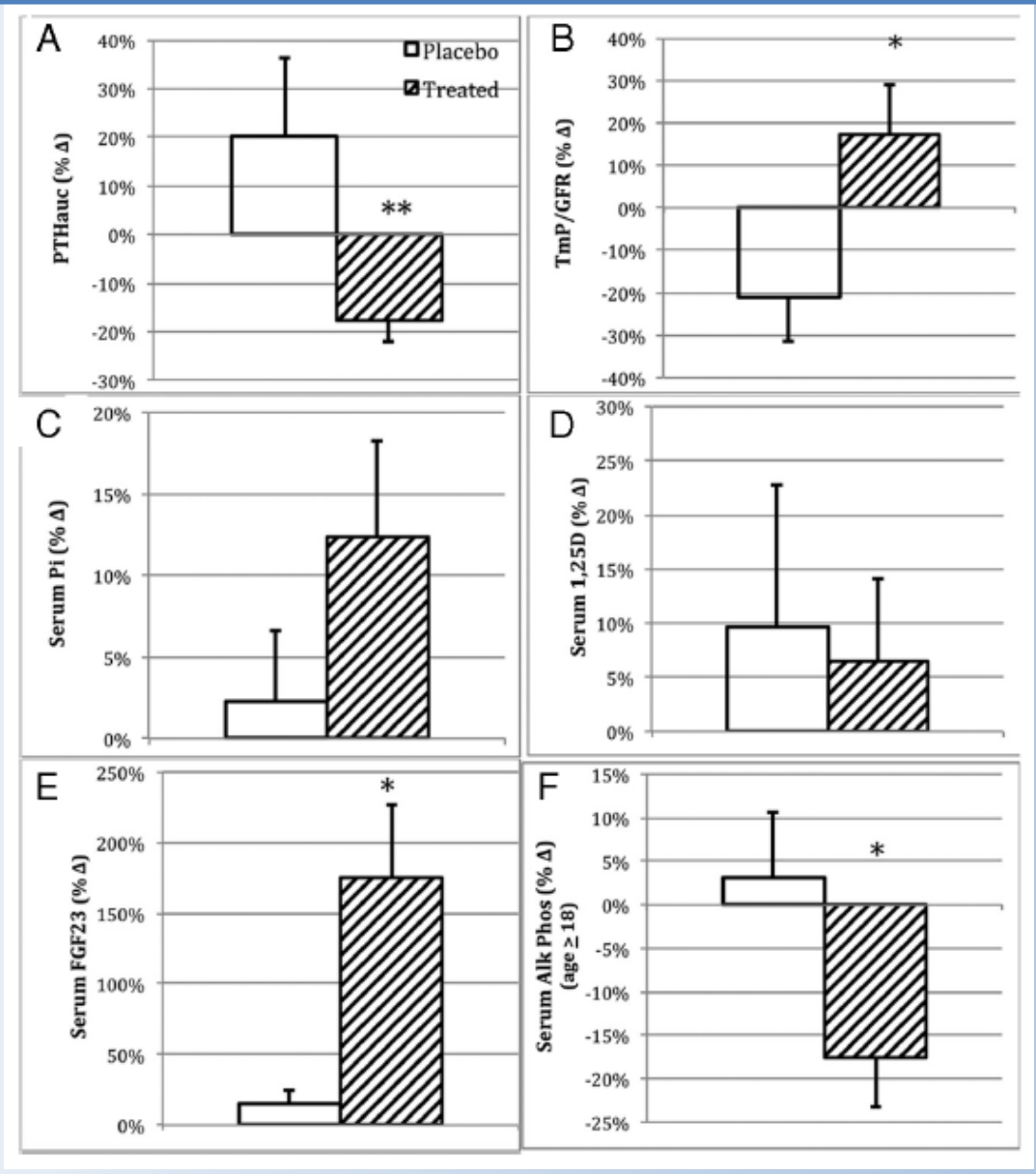
JCEM 99:3101, 2014

The hyperparathyroidism tends to get worse at night in XLH



JCEM 78:1378, 1994

In patients with significant 2ndary HPT, suppressing PTH with paricalcitol improves serum biochemistries and reduces bone turnover, despite a rise in FGF23



JCEM 99:3103, 2014

Suggested indications for conventional therapy in adults with XLH

PERSPECTIVE

JBMR

A Clinician's Guide to X-Linked Hypophosphatemia

Thomas O Carpenter,[1] Erik A Imel,[2] Ingrid A Holm,[3] Suzanne M Jan de Beur,[4] and Karl L Insogna[5]

- Spontaneous fractures
- Pending orthopaedic procedures
- Biochemical and/or radiographic evidence of severe osteomalacia
  - elevated Alk Phos (BSAP)
  - metacarpal, metatarsal, tibial compression tenderness
  - radiographic evidence of multiple or significant (e.g. femoral neck) insufficiency fractures
- Disabling bone pain

- JBMR 26:1381, 2011

Efficacy and Limitations of Conventional Therapy with calcitriol and phosphorus in Adults

Efficacy:

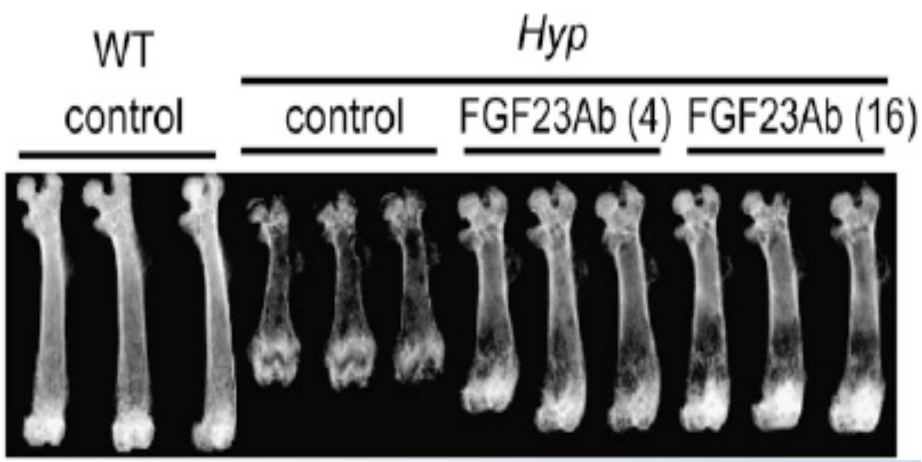
- Improves, but does not cure, osteomalacia. (JCEM 75:879, 1992)
- Appears to ameliorate dental disease. (JCEM, 100:3625, 2015)
- Anecdotally, reduces the risk of clinical fracture, accelerates healing of insufficiency fractures and healing after orthopedic surgery.
- If carefully monitored, can correct the hyperparathyroidism in XLH.

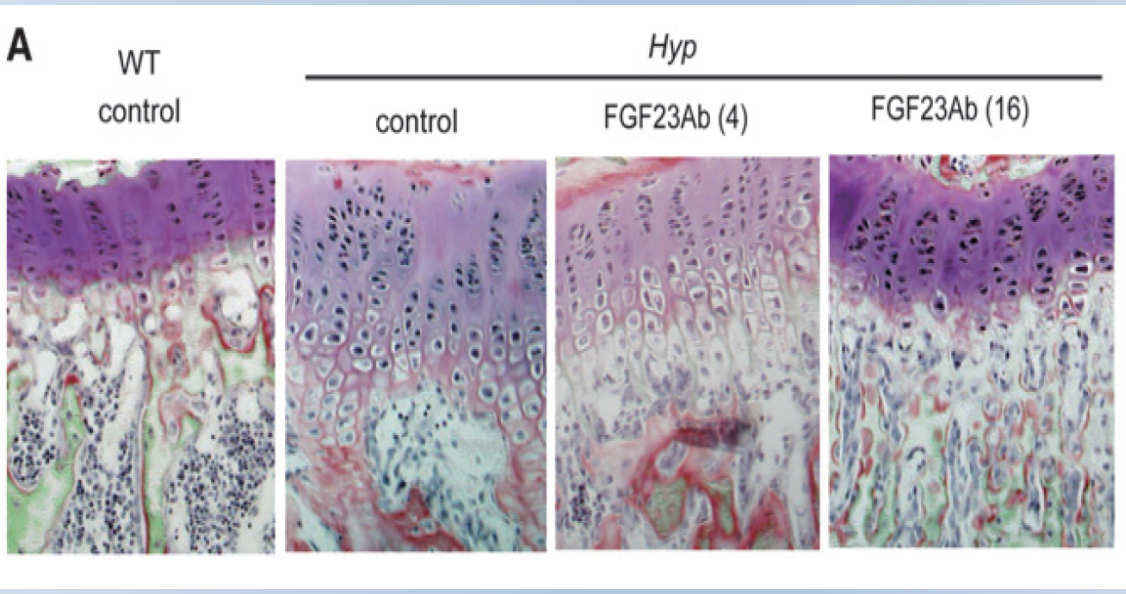
Efficacy and Limitations of Conventional Therapy with calcitriol and phosphorus in Adults

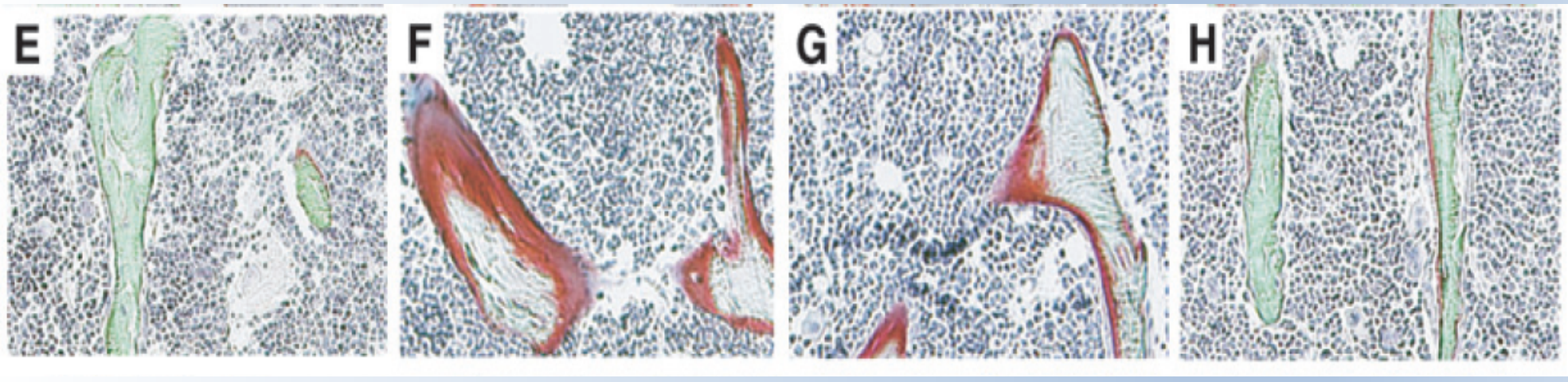
Limitations:

- Adherence is difficult.
- Proper management requires frequent visits and dose adjustments, so sub-optimal monitoring is often a problem.
- Does not improve linear growth in children, which obviously impacts adult height.
- Does not prevent dental disease.
- Does not prevent hearing loss or enthesopathy.
- Frequently accompanied by complications, including secondary and even tertiary hyperparathyroidism and nephrocalcinosis.

In a preclinical model of XLH (the Hyp mouse), an inhibitory antibody to FGF23 normalized serum Pi and 1,25($OH_{)2}$D levels and markedly improved bone growth and size… and healed the osteomalacia and growth plate abnormalities.



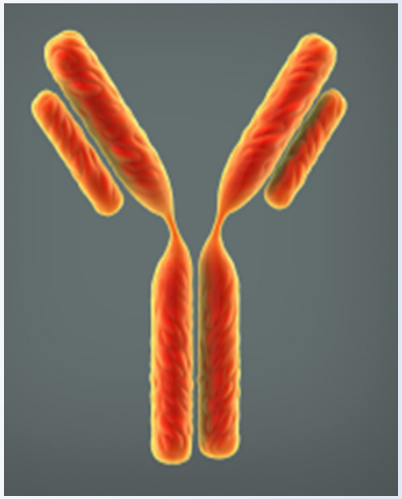




ale Bone Center

ASBMR

JBMR 24:1879, 2009



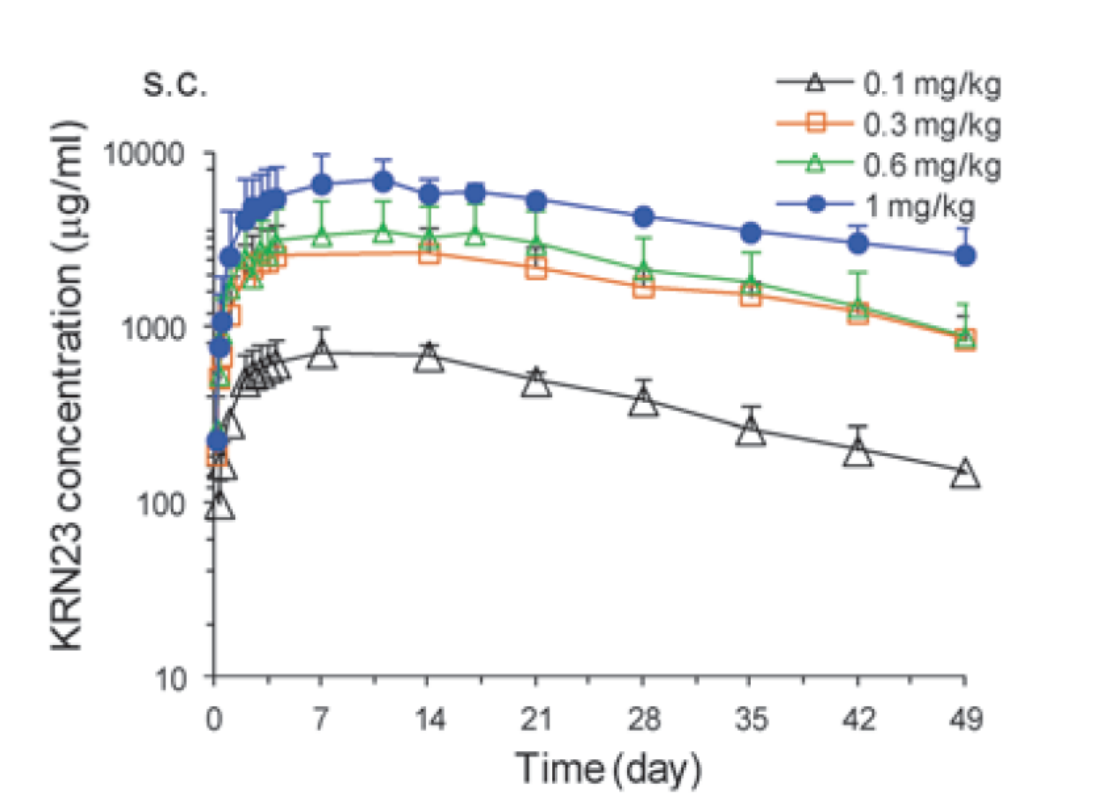
KRN 23: an inhibitory antibody to FGF23

- Kyowa Kirin Pharmaceutical Development, Inc. (KKD) has developed a recombinant human IgG_1 monoclonal antibody to FGF23 that has been tested in phase 1 and phase 2 clinical trials in children and adults with XLH.

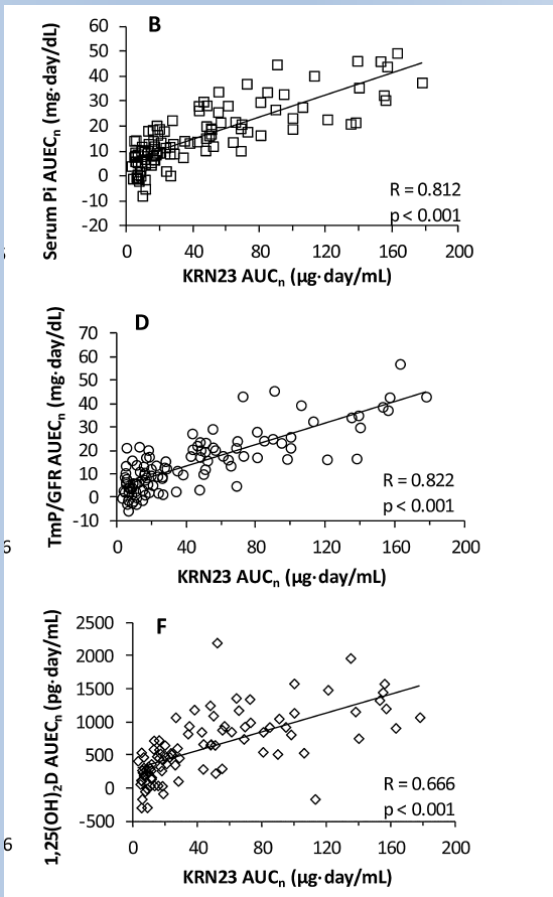
- Ultragenyx, in partnership with KKD, has ongoing fully enrolled phase 2 extension and phase 3 registration trials in adults with XLH.

Pharmacokinetics and Pharmacodynamics of KRN23

PK



PD



T_{max}: 7.0 to 8.5 days, $T_{1/2}$: 16.4 days

J.Clin. Invest. 124:1587, 2014
J Clin Pharmacology 56: 176, 2016

ale Bone Center

ASBMR

What types of patients are enrolling in the ongoing clinical trials with KRN23?

An adult patient in the phase 3 registration trial

30 yo female ICU nurse whose mother has XLH. Randomized 19-Feb-2016

Sporadically treated with calcitriol and phosphorus from 6mo -6yrs (adherence was a limited by financial constraints).

Ages 12-13: bilateral femur and tibial osteotomies.

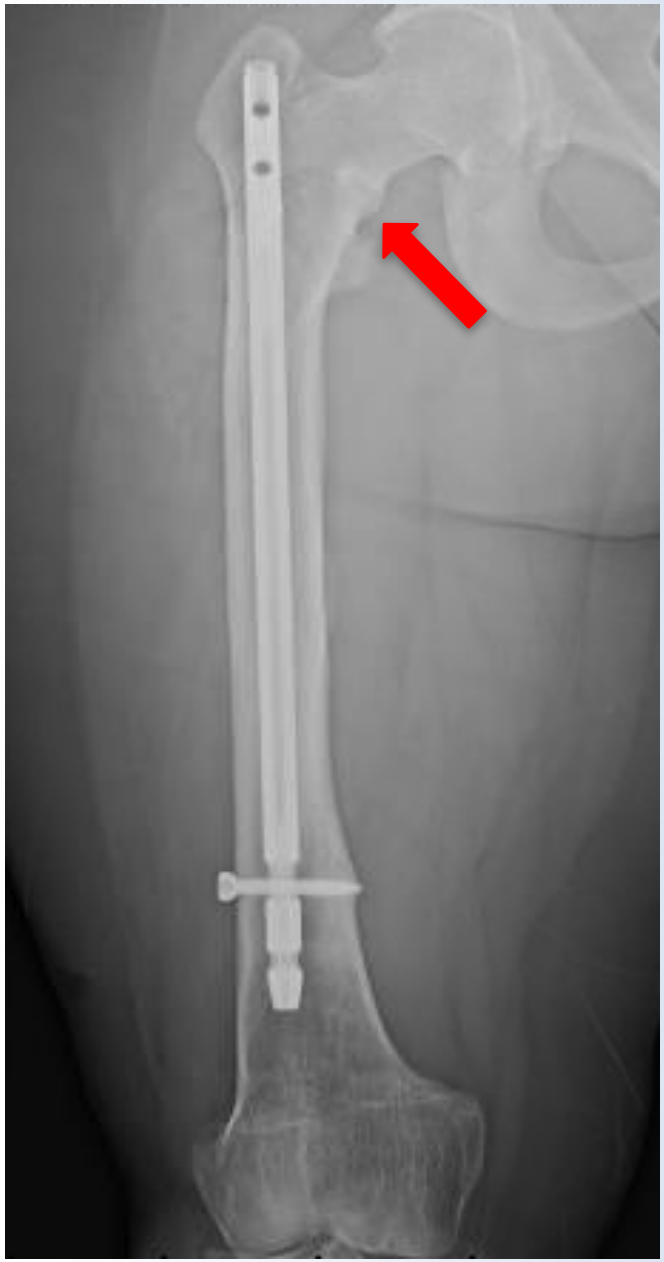
Ages 13-20: took medication with varying adherence.

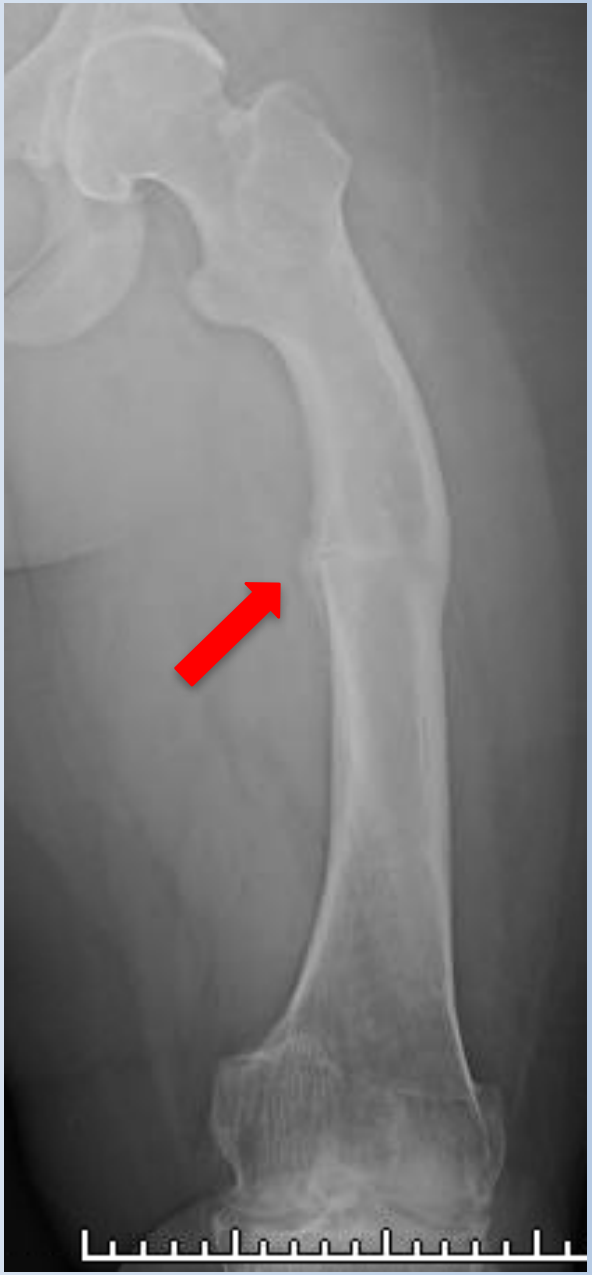
Ages 20-27: off therapy developed a left femoral stress fracture.

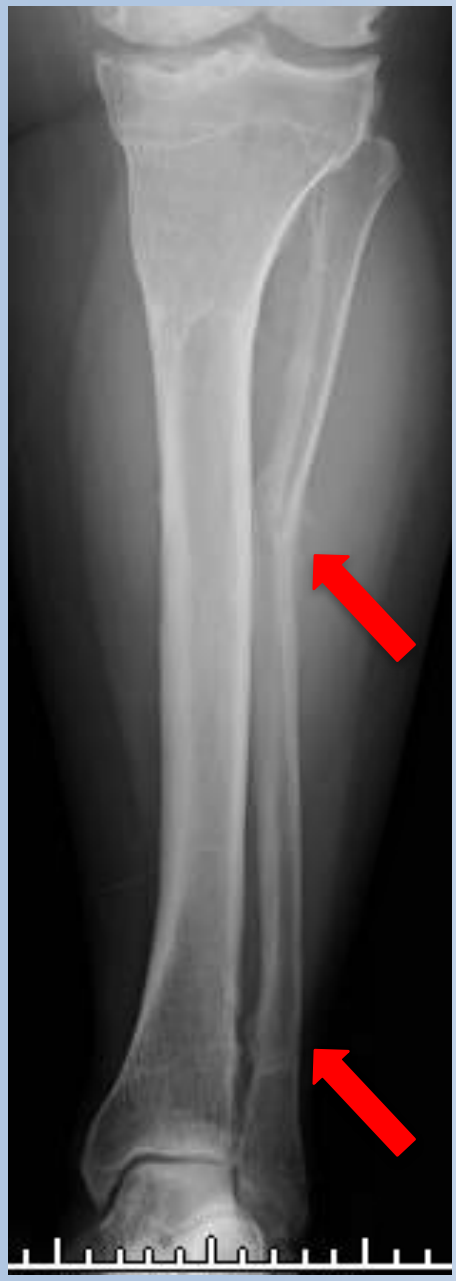
Age 27: therapy resumed phosphorus 2250 mg/d and calcitriol 0.25 mcg/Mon-Wed-Fri.

Age 30: (6 months before study entry) noted to have severe 2ndary HPT and advised to reduce phosphorous to 1000 mg/d and increase calcitriol to 0.25 mcg BID.

- Serum calcium: 9.5 mg/dL
- Serum phosphorous: 1.0 mg/dL; TmP/GFR: 1.0mg/100 mL GF
- PTH: 91 pg/ml (10-69 pg/ml)
- eGFR: > 60 mL/min
- Bone-Specific Alk Phos: 17 (3-19 ng/ml)
- Intact FGF23: 169 pg/ml







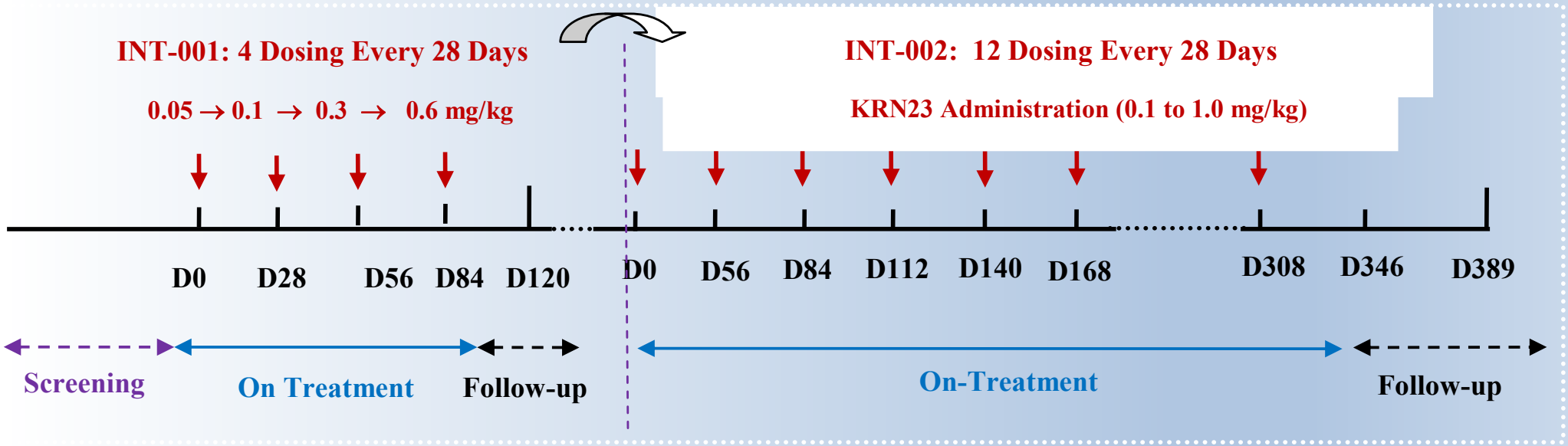
ale Bone Center

ASBMR

Data from the ongoing and completed studies with KRN23

Data from Adult Studies with KRN23

Cumulative 4-Month Dose Escalation (KRN23-INT-001) and 12-Month Long-Term Extension Study (KRN23-INT-002) in Adults with XLH

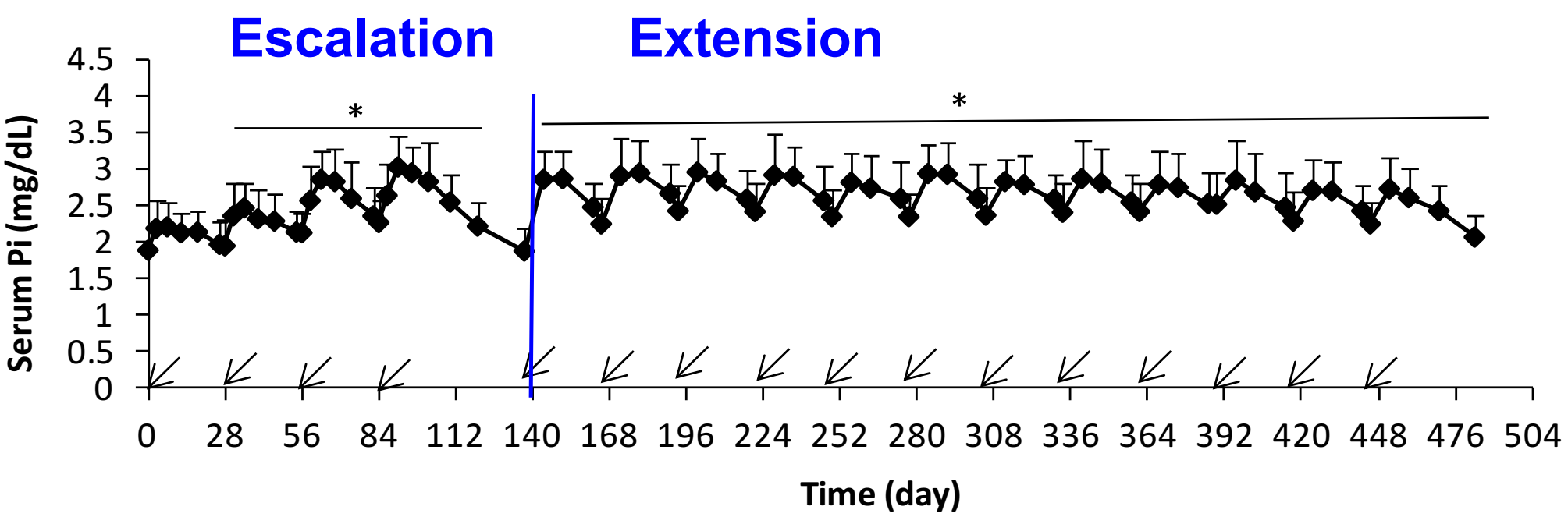


- Dose escalation: 28 adults with clinical diagnosis of XLH
- Age ≥ 18 years, intact FGF23 ≥ 30 pg/mL, TmP/GFR < 2.0 mg/dL
- Creatinine clearance ≥ 60 mL/min, serum calcium < 10.8 mg/dL
- Extension: 22 subjects enrolled in the extension study

ale Bone Center

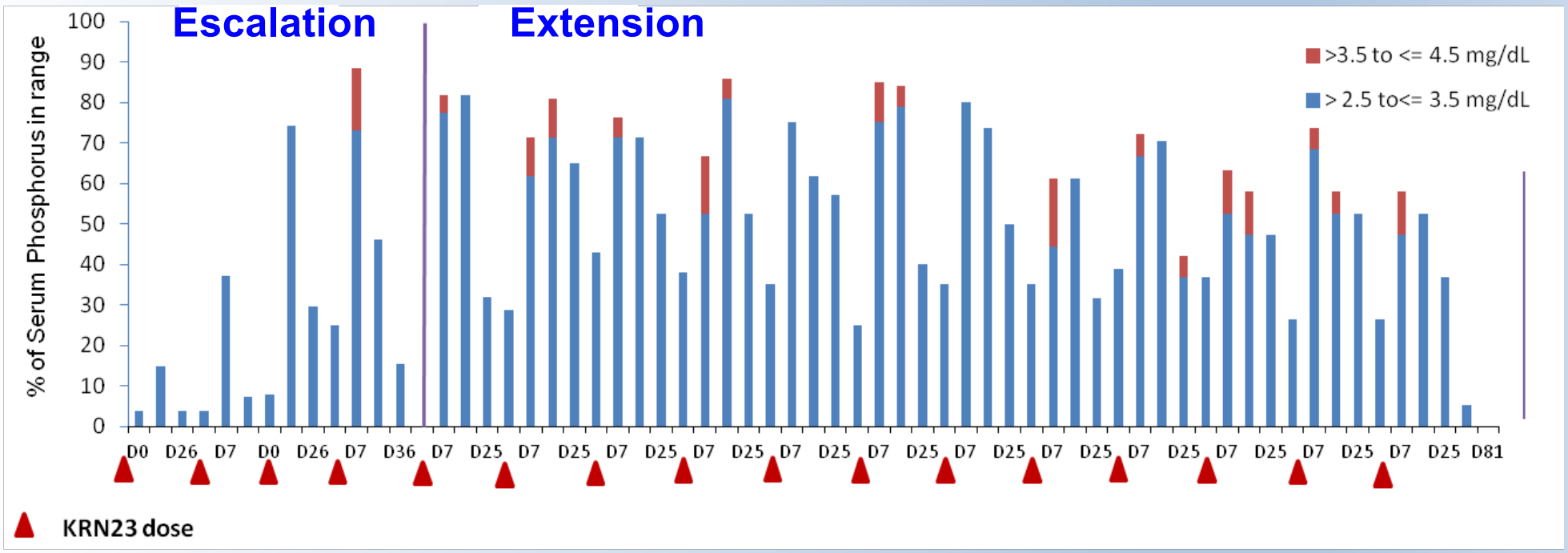
ASBMR

Effect on serum phosphorus



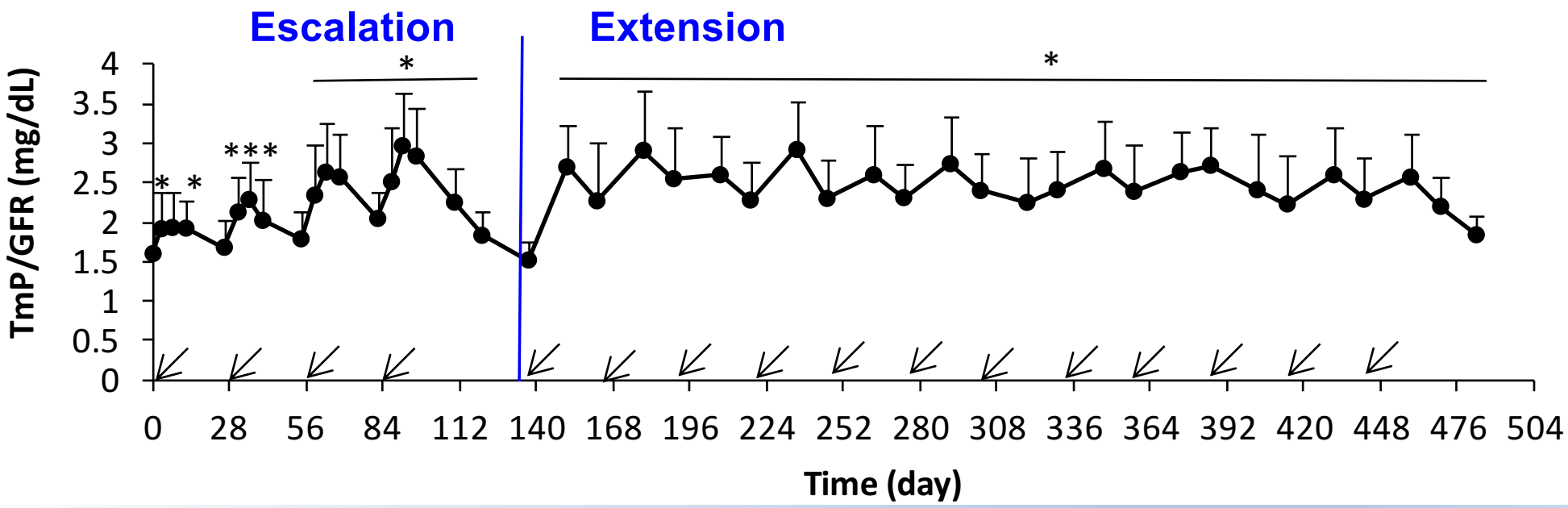
- Serum Pi peaked on Day 7 - 14
- Escalation: serum Pi increased as dose increased
- Extension: serum Pi increased after each dose and returned toward pre-dose level by next dose
- Fluctuations between peak and trough serum Pi levels were small after each dose (range: 9.97% - 21.5%)

Effect on serum phosphorus (cont.)



- During each dosing cycle of the extension study, peak serum Pi reached target range:
  - > 2.5 and ≤ 3.5 mg/dL in 44.4% - 81.8% of subjects
  - > 3.5 to ≤ 4.5 mg/dL in 4.5% - 16.7% of subjects
- Serum Pi did not exceed 4.5 mg/dL in any subject

Effect on TmP/GFR

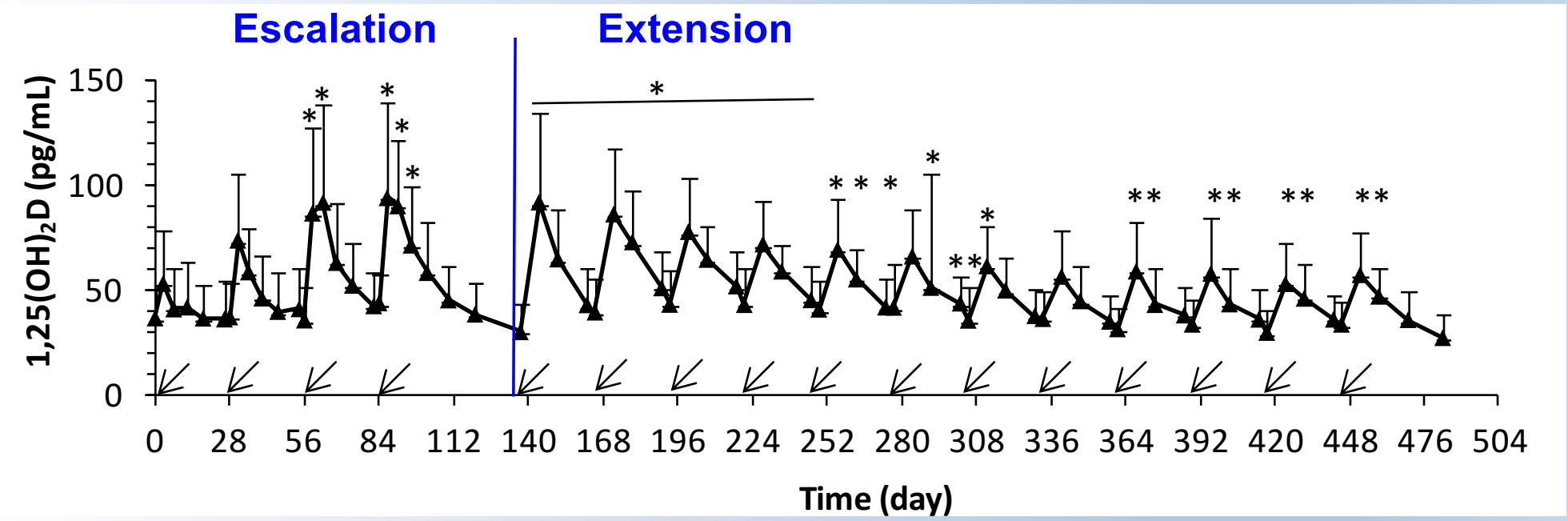


- TmP/GFR peaked on Day 7- 14
- Escalation: TmP/GFR increased as dose increased
- Extension: TmP/GFR increased after each dose and returned toward pre-dose level by next dose

ale Bone Center

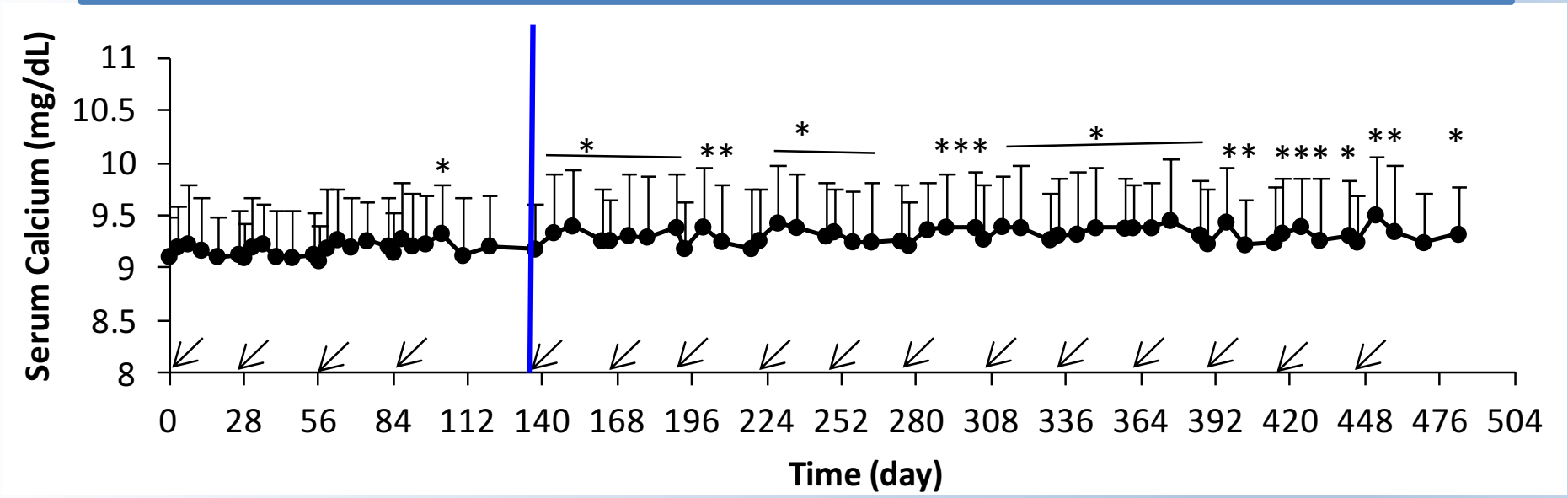
ASBMR

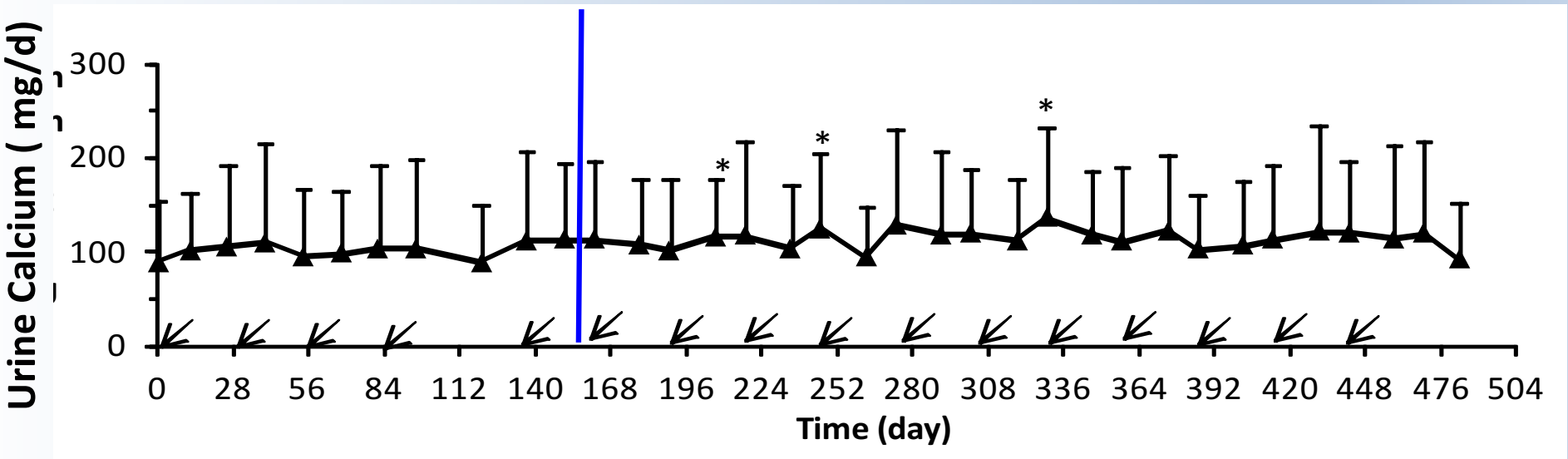
Effect on $1,25(OH_2D)$



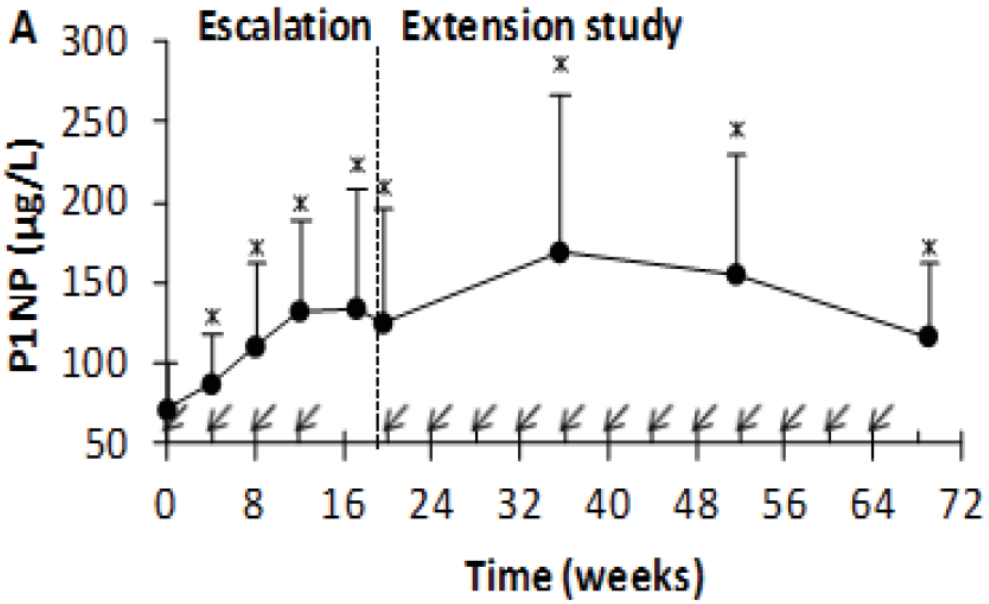
- Serum $1,25(OH)_2D$ peaked on Day 3- 7
- Escalation: serum $1,25(OH)_2D$ increased as dose increased
- Extension: serum $1,25(OH)_2D$ increased after each dose and decreased toward pre-dose level by next dose, with tendency to decrease over time

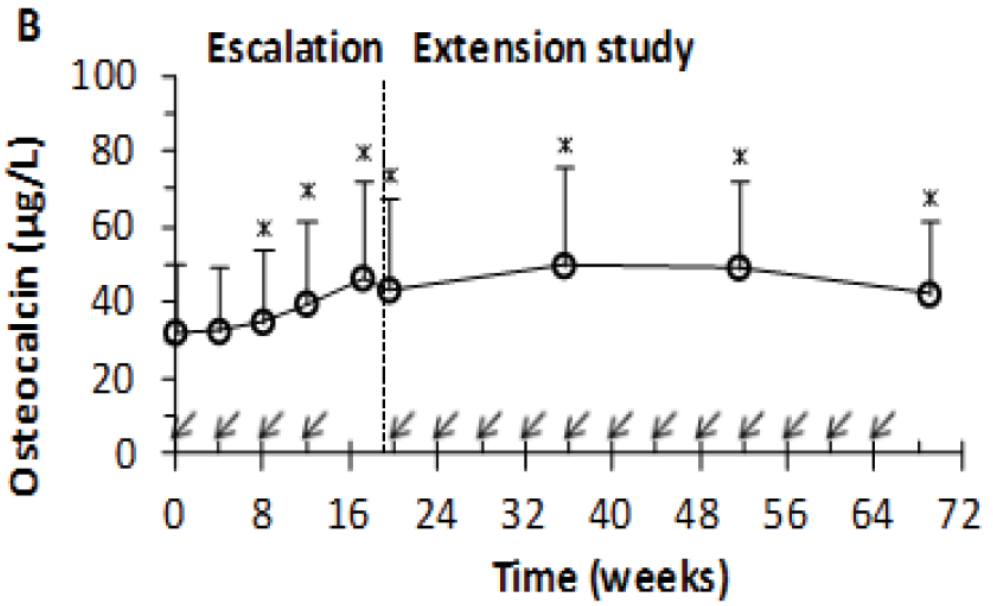
Effects on serum calcium and urine calcium

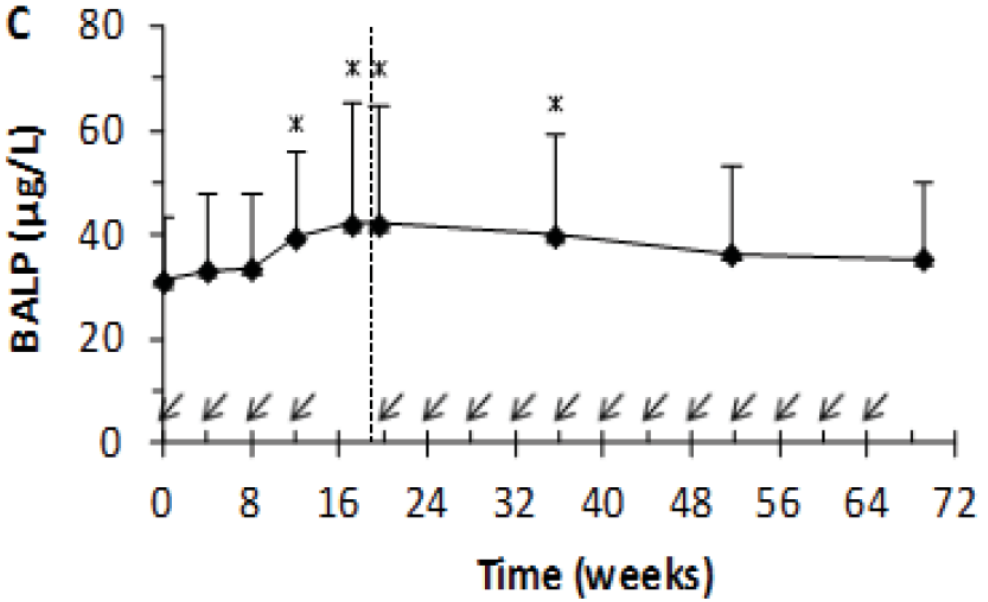


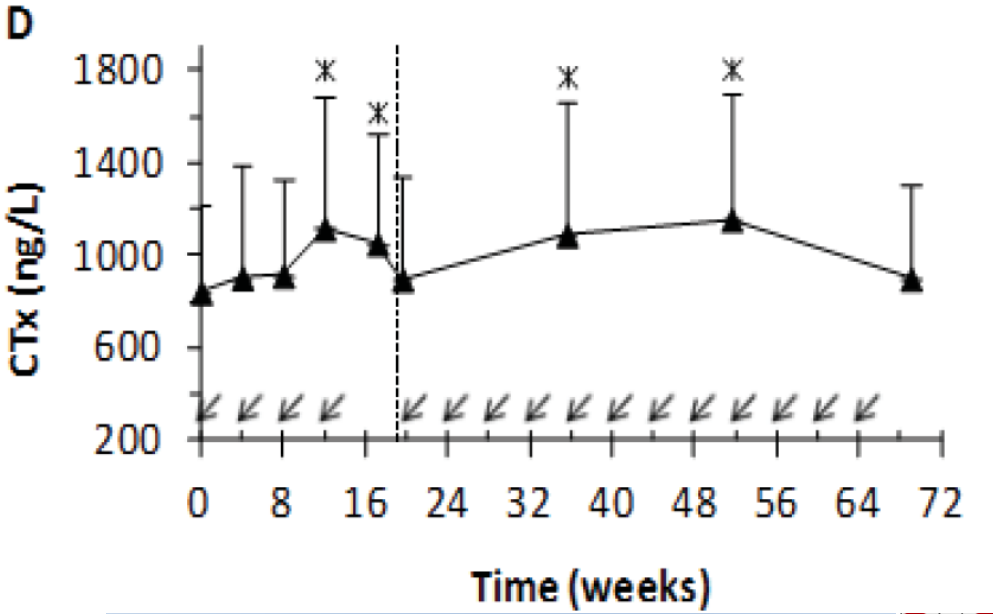


Effects on bone turnover markers







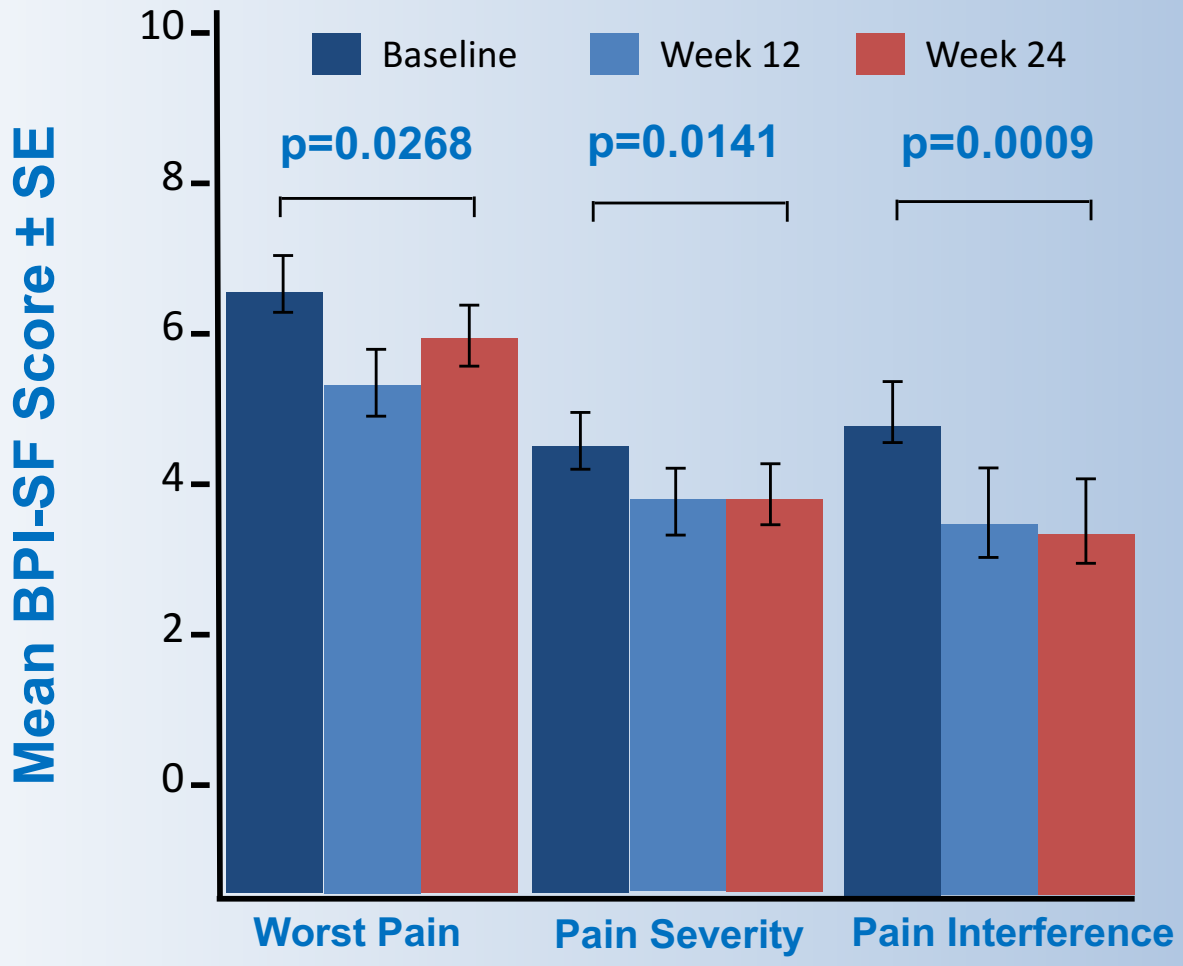


ale Bone Center

ASBMR

Do these study subjects feel better?

Improvement in Brief Pain Inventory Short Form Scores Overall

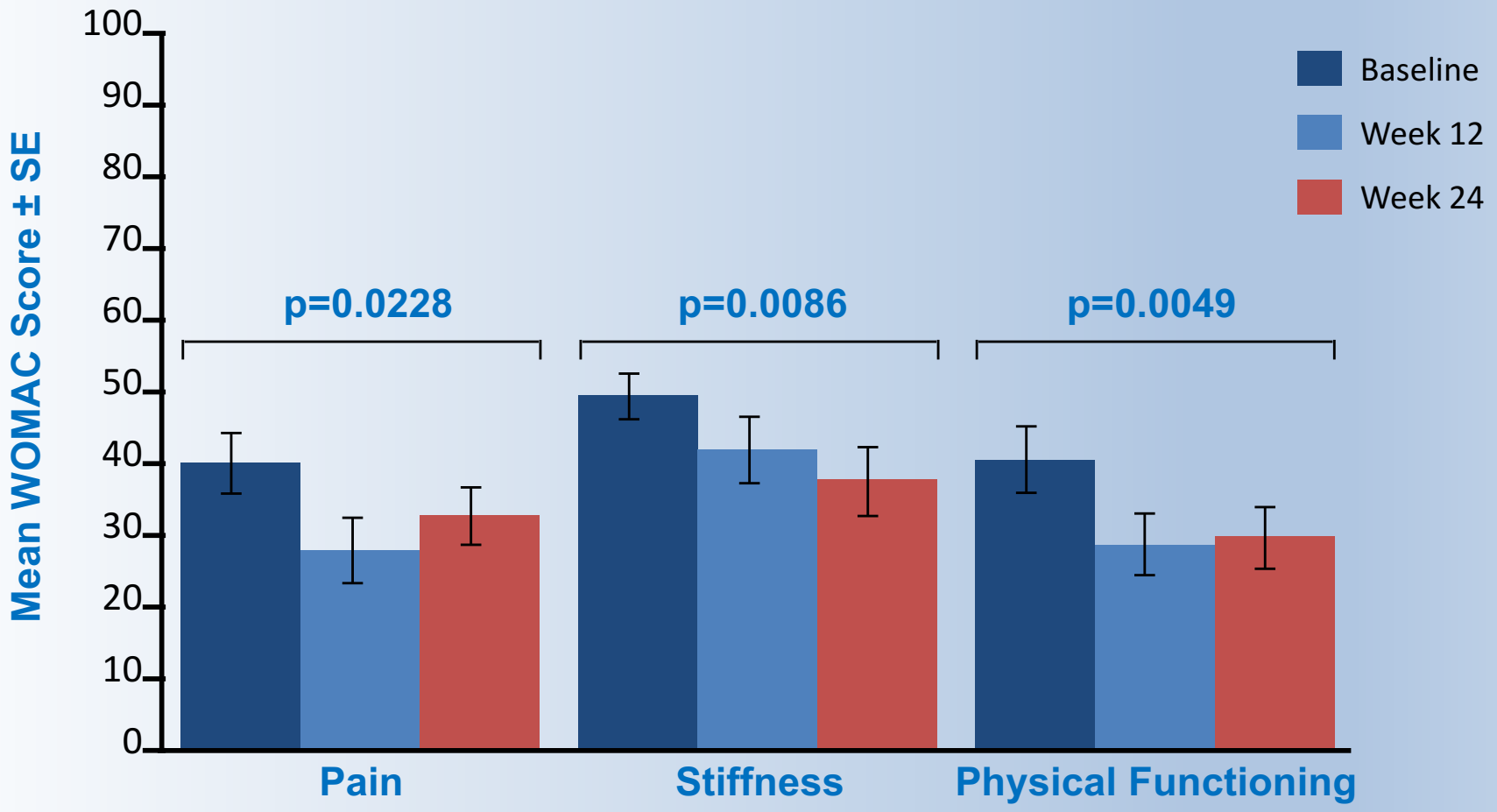


Ruppe et al, Poster #MO0319
Monday, 9/19 12:30pm-2:30pm
Expo Hall A1

ale Bone Center

ASBMR

Improvement in WOMAC Scores



Ruppe et al, Poster #MO0319
Monday, 9/19 12:30pm-2:30pm
Expo Hall A1

ale Bone Center

ASBMR

Improvement Balance and Agility (TUG test) and Walking Ability (6MWT)

Parameter	Baseline	Week 24	Mean Change	P value
Mean TUG test value, seconds (range)	12.8 (6.2-24.9)	11.0 (6.3-18.6)	-2.0	0.04
6MWT				
Mean actual distance walked, meters (range)	322 (80-639)	348 (160-592)	+25	0.05
Mean percentage of predicted distance, % (range)	49 (13-97)	53 (25-90)	+4	0.04
Values as mean (range) as indicated. 6MWT, 6 Minute Walk Test; TUG, Timed Up and Go				

Ruppe et al, Poster #MO0319
Monday, 9/19 12:30pm-2:30pm
Expo Hall A1

ale Bone Center

ASBMR

Summary of Phase 2 Adult Study

- KRN23 restored phosphate homeostasis in adult patients with XLH.
- Blocking FGF23 activity by SC administration of KRN23 every 28 days for up to 16 doses demonstrated good efficacy and a favorable safety profile.
- Participants are feeling better in the extension study.
- Based on these data, a phase 2 extension study and a fully enrolled phase 3 registration trial are ongoing in adults with XLH.

Follow up on our subject in the Phase 3 double blind, placebo-controlled adult study

- By May 2016, she was feeling more fatigued and felt that her muscles were “weaker.” Her lower back was bothering her more. Her hips were not more symptomatic.

- She ended the double-blind portion of the study 8 Aug 2016 and has received two doses of KRN23 in the open label phase of the study: the first on 8 Aug 2016, the second on 7 Sept 2016.

- She is feeling markedly better. She feels stronger, has more energy, and less pain. She has to stop much less often to rest at work and when she resumes working no longer feels stiff.

The Future

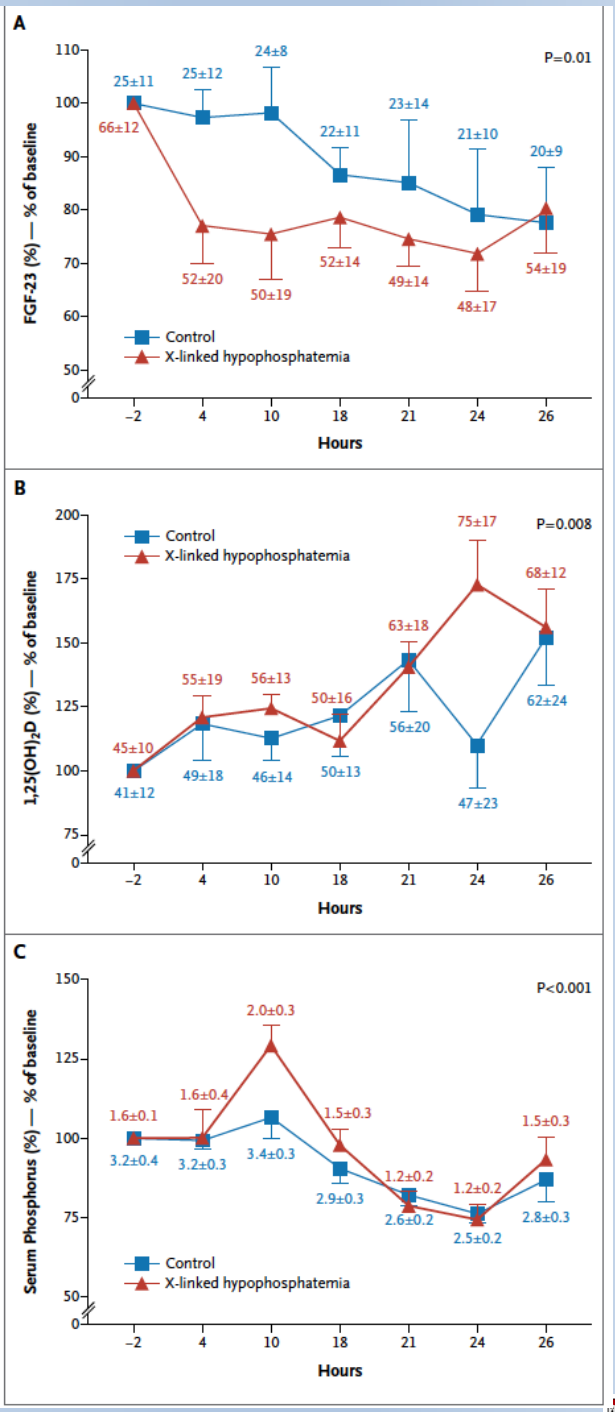
There are several other genetic disorders, in addition to XLH, that are caused by excess FGF23 and which might be amenable to treatment with KRN23:

Disease	Gene
• Autosomal dominant hypophosphatemic rickets	FGF23
• Autosomal recessive hypophosphatemic rickets 1	DMP1
• Autosomal recessive hypophosphatemic rickets 2	ENPP1
• Epidermal nevus syndrome	HRAS/NRAS
• Raine syndrome related hypophosphatemia	FAM20C

Back to the Future

We may have something to learn from calcitonin's effects on the osteocyte.

Calcitonin appears to be the only drug that actually lowers circulating levels of FGF23 in XLH, at least transiently.



NEJM 364:17, 2011

Summary

- XLH is a life-long disease. The notion that treatment is not warranted after epiphyseal closure is an oversimplification.
- Many of the most debilitating complications of this disease occur in adults.
- Among these are: bone pain, insufficiency fractures, arthritis, dental disease, hearing loss, frequent secondary hyperparathyroidism and, most especially, enthesopathy.
- Conventional therapy with calcitriol and phosphorus requires meticulous management by the health care provider and good adherence by the patient, which is difficult to achieve. However, within those limitations conventional therapy can improve bone pain, ameliorate dental disease and likely speed healing of fractures.

Summary (cont.)

- Conventional therapy cannot affect the progression of hearing loss or enthesopathy, nor does it appear to affect the symptoms of fatigue and weakness.
- In addition to having a more sound therapeutic rationale, thus far KRN23 appears to be superior to calcitriol and phosphorus in correcting the biochemical abnormalities and improving functional status in XLH.
- Whether it will prevent or ameliorate the long-term complications of this disease will have to await a much longer clinical experience.
- It would be ideal if strategies could be devised to suppress FGF23 production by the osteocyte.

Acknowledgements

These studies would not be possible without:

- **Investigators and research staff at:**

  Yale University, Connecticut
  Indiana University, Indiana
  Duke University, North Carolina
  University of Texas-Houston
  University of California San Francisco, California
  Shriners Hospitals for Children, Missouri
  Shriners Hospital for Children, Montreal
  University of Groningen, The Netherlands
  Le Kremlin Bicêtre, Paris, France
  Birmingham Children's Hospital, UK
  Royal Manchester Children's Hospital, UK
  Great Ormond Street Hospital, UK

ale Bone Center

ASBMR

Acknowledgements

These studies would not be possible without

- The sponsorship of ***Ultragenyx*** in partnership with ***Kyowa Kirin Pharmaceutical Development, Inc.***

  Javier San Martin
  Matthew Mealiff

and

- The altruism of the volunteers with XLH who give of themselves to make this work possible

Thank you for your attention!

ale Bone Center

ASBMR